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DRUG MISUSE AMONG THE ELDERLY AND ITS IMPACT ON COMMUNITY-BASED CARE

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN SERVICES

OF THE

SELECT COMMITTEE ON AGING
HOUSE OF REPRESENTATIVES

ONE HUNDRED FIRST CONGRESS

FIRST SESSION

APRIL 19, 1989

Comm. Pub. No. 101-718

Printed for the use of the Select Committee on Aging

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DRUG MISUSE AMONG THE ELDERLY AND ITS IMPACT ON COMMUNITY-BASED CARE

WEDNESDAY, APRIL 19, 1989

U.S. HOUSE OF REPRESENTATIVES,
SELECT COMMITTEE ON AGING,
SUBCOMMITTEE ON HUMAN SERVICES,
Washington, D.C.

The subcommittee met, pursuant to notice at 10:07 a.m., in Room B-318, Rayburn House Office Building, Hon. Thomas J. Downey (chairman of the subcommittee) presiding.

Members present: Representatives Downey, Snowe, Duncan and Saiki.

Staff present: John Olinger, Majority Staff Director; Moya Benoit, Majority Research Assistant; Sean Hornbeck, Staff Assistant; Natalie Cannon, Minority Staff Director; and Dari Minzner, Minority Research Assistant.

OPENING STATEMENT OF CHAIRMAN THOMAS J. DOWNEY

Mr. DOWNEY. The subcommittee will come to order.

Before we hear from our fine witnesses, they will have to hear from us. We will try to make that as painless as possible.

It is my pleasure today to open this hearing entitled "Drug Misuse Among the Elderly and Its Impact on Community Based Care." As Chairman of the Subcommittee on Human Services, I would like to thank the Member who is present here today and the witnesses who are with us as well.

This hearing addresses a growing problem in this country: drug misuse and mismedication among the elderly. This has been an ongoing concern of the House Select Committee on Aging since 1982 when hearings were held on the subject by its then Chairman, Claude Pepper. This hearing could also be viewed as an oversight hearing on the provision in the Medicare Catastrophic Coverage Act that mandates the Department of Health and Human Services to establish a drug utilization review. That has special importance to me not only as chairman of this subcommittee, but also as Acting Chairman of the Subcommittee on Human Resources of the House Ways and Means Committee.

The Inspector General of HHS, Richard Kusserow, who is with us today, has called the problem of drug misuse among the elderly as "the Nation's other drug problem" in his recently released report, which we will be focusing on in this hearing.

Among the findings of the Inspector General's report are two important facts: first, although Americans age 60 and over comprise only 17 percent of the total U.S. population, they account for 30 percent of all hospitalizations and 51 percent of deaths from drug reactions; and second, the problem is likely to grow unless an effective drug utilization review is implemented.

Prescription drugs are, for millions of older Americans, a fact of life. Older people take an average of about 15 prescriptions per year, and often they must take several drugs simultaneously, which makes them more vulnerable to adverse drug reactions. These reactions are often made worse because aging increases sensitivity to certain other medications.

The causes of this problem are varied: one, the lack of geriatric knowledge on the part of the physician when prescribing for the elderly; two, the patient's noncompliance in following the proper instructions; three, the high cost of prescription drugs; and finally, the lack of formal guidelines from the Food and Drug Administration for premarket clinical testing of drugs for elderly patients.

Nationally, approximately 1.6 billion prescriptions are written for over 30,000 different drugs each year. Over one-third of these are for older adults. About 200 new drugs are approved each year. These numbers are simply staggering. The Food and Drug Administration is charged with the responsibility of protecting the health and safety of the American people, and that includes the oversight of premarket drug testing and post-market monitoring of drugs.

We will be hearing testimony today from Commissioner Young of the Food and Drug Administration, and we have asked that the Commissioner supply the subcommittee with the status of these guidelines which we understand were drafted 6 years ago but have yet to be published. That answer is the heart of our hearing. It is an issue that has already been identified and reidentified by this committee, by the Senate Special Committee on Aging, and by consumers all around the country.

We understand that guidelines of some type are already being implemented by certain members of the pharmaceutical industry. However, there is a need for a uniform set of standards to be set for the industry by the FDA if the FDA is to meet its responsibilities of protecting the health and safety of Americans where medical practices are concerned.

We are hopeful that Commissioner Young will have something to report today that will give not only the pharmaceutical industry but also the elderly some sense of progress in our effort to prevent future adverse drug reactions.

We note that the FDA has published a proposed guideline for format and content of the Clinical Data section of a New Drug Application which involves favorable and unfavorable responses to age and to conditions common in older patients. However, it is our strong belief that the FDA should not be naive enough to think that the entire pharmaceutical industry will develop and follow informal elderly drug testing guidelines themselves. We feel that there must be a formal requirement that elderly people be included in premarket testing by all pharmaceutical manufacturers. Claiming that the industry knows about the guidelines does not necessarily mean they are in place. It is my belief that these guidelines are necessary if we are to have an effective drug utilization policy, and

I believe it is time for the FDA to stop stonewalling and release them.

In my home State of New York, there are currently 3 million people over the age of 60. This equals approximately 18 percent of the total population. About 42,000 of these elderly have been involved in drug-related emergencies in hospitals in New York. Because the number of elderly is expected to rise steadily, we can only assume that unless timely, preventative measures are taken, so, too, will the number of drug-related emergencies or deaths. In addition, the number of elderly living alone is rising. These elderly could be living with a killer in their own homes, with no way to recognize it.

There is no doubt that there is much to be done if we are to decrease the number of illnesses or deaths due to adverse drug reactions. In addition to the guidelines being published by FDA, there is a great need to find more ways to further educate physicians and pharmacists in the treatment of elderly people, both practicing and those studying to be. Physicians need to work together with pharmacists in the care of the elderly patients. Perhaps better labeling policies with warnings in large print for the elderly would be helpful.

The elderly themselves need to be educated further about the possibility of adverse reactions to the drugs they are taking, and they should not be intimidated or afraid to discuss their medical concerns with their doctors. State and area agencies on aging and all service providers should provide materials to those elderly that they serve in order to supply them with information about ways to prevent drug misuse. Millions of seniors who receive meals at congregate sites and senior centers throughout the country by way of the Older Americans Act receive nutritional information with their meals. Why not drug education as well? The Federal Government must team up with the Department of Health and Human Services and the Administration on Aging to develop a better method for preventing drug misuse and mismedication among the elderly.

Now is the time for attention to be focused on this problem. When the drug prescription benefit kicks in next year as part of the Medicare Catastrophic Health bill, a whole new dimension will open up for seniors who will be affected. It is imperative that the necessary safeguards be put into place now so that future tragedies will be prevented. The elderly's medicine cabinet should not be a pharmacological "Pandora's box".

Today's group of witnesses represents a wide array of concerns about this particular problem, and we look especially forward to their presentations today.

Ms. Snowe.

STATEMENT OF REPRESENTATIVE OLYMPIA J. SNOWE

Ms. SNOWE. Thank you, Mr. Chairman. I am very pleased to be able to be here to participate in this hearing concerning drug use and mismedication among the elderly.

I want to commend you, Mr. Chairman. I think you have given an excellent outline of the problem before this committee, and I commend you for calling this hearing today to examine these critical problems which often not only adversely affect the lives of older Americans but, indeed, threatens them.

This hearing is also particularly timely as it gives us the opportunity to examine the potential for a more comprehensive solution, utilizing the full range of private as well as Federal resources. Older Americans consume a high rate of prescription drugs, nonprescription drugs, and suffer a correspondingly high rate of adverse reactions to those drugs. They are more sensitive to medications and are more likely to have multiple, independent prescriptions.

As a result of this vulnerability, let's take, for example, the case of a 73-year-old woman in my State of Maine who was taken to the emergency room after her daughter, who lives out of State, asked the local area agency on aging to investigate. She was found to be on 12 medications, five of which were diuretics and two tranquilizers, all prescribed by the same physician. Fortunately, the situation was resolved by her daughter, as well as the area agency on aging and the local quality assurance team.

Today's witnesses represent a wide range of experts involved in investigating the causes of mismedication problems and proposing, developing and administering programs to deal with it. As we move forward to implement the prescription drug benefit under the Medicare Catastrophic Coverage Act, solutions become even more critical.

I think also, given the problems that are surrounding this issue, it is absolutely vital that the Food and Drug Administration issue the guidelines on drug testing in clinical studies in the use of elderly. It seems to me imperative that it's long overdue. It's been a problem since the early 1980's, as the Chairman has indicated, and we recognize that the solutions to these problems are long overdue.

Again, Mr. Chairman, I thank you for holding this hearing today.

Mr. DOWNEY. Thank you, Ms. Snowe.

We also want to welcome our colleague, Mr. Duncan of Tennessee. John, do you have a statement you would like to make?

Mr. DUNCAN. Mr. Chairman, I don't have any statement. I know probably less about this problem than anybody in this room here today, so I am here mainly to learn and listen to the testimony. It is a great honor for me to be a member of this committee now and to be here with two of the more highly-respected Members of the House, Congressman Downey and Congresswoman Snowe. So I'm just going to listen to the witnesses and try and learn a little something.

Thank you very much.

Mr. DOWNEY. Thank you, John. At this time, if there are no objections, I would like to submit the prepared statement of our colleague, Congresswoman Morella, for the hearing record. Hearing no objections, so ordered.

[The prepared statement of Representative Constance A. Morella follows:]

PREPARED STATEMENT OF REPRESENTATIVE CONSTANCE A. MORELLA

Mr. Chairman, thank you for the opportunity to participate in this hearing to address the problem of drug misuse among the elderly. The problem is of such significance that I hope to schedule a field hearing in my district in June to assess the impact in the community.

As important as drugs are to modern health care, they can be prescribed, dispensed, and used inappropriately. This can have especially serious consequences for the elderly, who are more frequently ill, suffer more from chronic conditions, and consume more medications than other populations. Experts believe that millions of elderly Americans are being overmedicated, resulting in adverse drug reactions and interactions, unnecessary health problems and even premature death.

Drug safety and efficacy have for some time been within the purview of the Federal Government. There are many reforms needed to ensure that mismedication of the elderly is reduced. It is particularly relevant that we address this issue prior to implementation of the prescription drug related provisions of the Medicare Catastrophic Coverage Act. I look forward to learning more from the distinguished panel of witnesses we have before us today.

Mr. **Downey**. Proceed, Mr. Kusserow.

STATEMENT OF RICHARD P. KUSSEROW, INSPECTOR GENERAL, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ACCOMPANIED BY MICHAEL MANGANO, ASSISTANT INSPECTOR GENERAL, DHHS

Mr. **Kusserow**. Thank you, Mr. Chairman. I am Richard Kusserow, the Inspector General for the Department of Health and Human Services. With me today is Michael Mangano, who is the Assistant Inspector General for Office of Analysis and Inspections, who has taken the lead on some studies we're doing in this area, including the one that we're focusing on today, the Medicare Drug Utilization Review that we recently performed. Of course, we will make that study available to the committee as we issue it.

Before elaborating on the study itself, with your permission, I would like to submit my entire statement for the record and highlight and maybe give some background and overview of what it is that we're trying to do.

Mr. **Downey**. Without objection, so ordered.

Mr. **Kusserow**. First of all, I am the Inspector General, not for the FDA, but for the entire Department of Health and Human Services. This means the perspective that I have looks across the entire biomedical landscape. It looks at the initiation of biomedical research through the National Institutes of Health or Alcohol, Drug Abuse and Mental Health Administration tracking a disease through the Center for Disease Control down at Atlanta, GA, looking at the whole drug and device approval process in FDA, and then, when you do, in fact, have drugs and devices approved, then the health care policy for payment through the Health Care Finance Administration for the elderly and infirm disadvantaged of America. So the view that I have is fairly broad in that respect. I think it's important to understand that having a more global viewpoint is important to try to get the big picture.

In that regard, it became clear to us last year, as Congress moved toward the passage of catastrophic health insurance, that something new was going to be added to the Medicare program in the form of a drug component that had not existed before.

In the initial surveying of the Department, it became clear that the Health Care Finance Administration had not focused a great deal on drug-related problems because it was not part of the payment system. Therefore, it seemed that what we needed to have is, before the full initiation of that program, an understanding as to where we are with regards to mismedication among the elderly, what it is we can do about it before we start actually paying for these kinds of services. Also, I think it gave us a unique opportunity to, in fact, engage what we hoped would be a benchmark effort against which we can measure progress in the future.

We have initiated a series of studies. The first one on Medicare drug utilization and review is, in fact, going to be followed by a number of other studies. We are doing a study on the whole area of community pharmacy counseling. As you will see in my comments, a major part of the controlling of the system against mismedication is with the community pharmacists, and we want to have a better understanding as to what happens in that arena. That is moving toward completion as well.

We also feel that it's very important that we look at the whole series of implications of privacy associated with the fact that we're going to be maintaining records. In one sense, we are trying to protect beneficiaries against mismedication by keeping some sort of record as to what kind of medication they're receiving and, therefore, be alert to drugs that might interact in a way that is adverse to the health of the beneficiary, but at the same time that means we are going to be collecting data. So what is it that we can do to protect the privacy and confidentiality of our beneficiaries by this new system of records that the Health Care Finance Administration is going to be developing, the new computerization to incorporate those records.

We are also very mindful of the fact that once you start paying a new drug benefit, we're going to have to be sure there is not abuse of that process, that, indeed, do we have adequate sanctioning tools to root out those individuals or entities that would engage in wrongful or abusive behavior with regards to our beneficiaries or programs. Therefore, we have as another separate study a survey and assessment of the adequacy of authorities for dealing with abuse cases.

Another study is to try to have a better understanding as to why it is that elderly Americans have a very high incidence of noncompliance with instructions with regards to their drug regimen. We need to have a better understanding of why that takes place. We do know that in over half the cases they do not follow the instructions of their physician or pharmacist. Now, why is that the case? So we have a separate study to try to understand that behavioral pattern.

We also have to have, I believe, an ongoing assessment of the Medicare prescription drug benefit and how that program is going to be implemented, what kind of system is it going to develop, how effective is it, is it going to meet the intent of the Congress, and that is going to be an ongoing effort as well.

Also, as a final point along that line, I would mention the fact that we have another study that is looking at the whole area of State pharmacy boards and how effectively they are dealing with pharmacists, who, in fact, are providing substandard service. And so that sort of rounds out about seven different major studies that we have ongoing, so now let me revert back to the one that is really at hand.

The overall purpose and aim of this study was to try to see if we could foster a better understanding as to what it is we are dealing with, where we have problems in the system, and perhaps identify where it is we might be able to take some good steps to improve the process, to make it more efficient, to have fewer cases of mismedication among the elderly.

Our findings attempt to describe widespread patterns of mismedication among elderly adults. We tried to identify those aspects of the drug therapy delivery system that have created this problem and then try to describe the Drug Utilization Review interventions that appear most promising and put it on the table for consideration.

In our review, what we did find was that there was, indeed, a widespread problem among adults, something that few would deny. We also found that, with the implementation of the Medicare prescriptions drug benefit, the utilization of drugs may, in fact, rise significantly. Now this, in turn, is probably going to cause an increased risk in mismedication. The one fact that I think almost all of your witnesses today will agree on is that the more medication you have, the more prescriptions you have, the greater the likelihood of mismedication, where you would have drugs that might interact in a way that has an adverse effect on the patient. So if you, indeed, increase the amount of prescriptions to the elderly, you're probably going to have an increase in the problem.

In addition, the problems with mismedication among the elderly reflects a series of what we find is systemic weaknesses throughout the whole drug therapy delivery system. You can start from the top and go right through the bottom, right to the point where the patient actually uses the medication, and I think you will find in all areas that you can have some improvements. We recognized that there has been enormous progress toward including the elderly in the clinical testing of drugs. However, we believe that further improvement needs to be done certainly at the manufacturers' level with respect to drug tests done prior to FDA approval, and the post-marketing experience on drugs used by the elderly needs to be captured, and we have to have a better realization as to the extent of the problem on that part of the spectrum.

We are, in fact, pleased that this last year, 1988, the Public Health Service did issue their final guidelines for clinical and statistical sections of the application process. That really focuses on the fact that they are required now in that process to look at age variables and to alert FDA when there's a problem. We are still urging, as I have heard the committee say as well, the expeditious issuance of the final FDA guidelines concerning the clinical trials on the elderly and labeling. What we're really looking for here is the exact statistical mix that should be involved in determining what effect drugs would have on the elderly part of our population.

We noticed that at the physician level we found that there was inadequate training and education for physicians in the area of geriatric pharmacology. This leads to prescribing patterns that are not necessarily in the best interests of the elderly adults. We found that in 1988 less than 2percent of medical students enrolled were required to take courses in geriatrics. We also found that most physicians only had one course in pharmacology. This combination, I think, does not bode well in terms of not having high error rates in the way medications are prescribed for the elderly, so we think there is a lot of improvement needed on that front.

We even looked at the pharmacy level and we found that, notwithstanding the fact that your professional associations of pharmacists require drug counseling as part of their duties, and that 16 States, in fact, mandate it—16 State pharmacy boards mandate drug counseling—what we really did find was that that is not being done, that only a small percentage of the elderly patients receive drug counseling, and that is even when it's mandated under the law.

This problem is further complicated by the fact that many pharmacists do not really perform adequate reviews of patient drug regimens or consult with physicians and patients where potential problems of conflicting drugs are identified. We think this goes back to the catastrophic health insurance program, which is going to enable us to set up a system of drug utilization review.

One of the things that we are urging in our report for the Health Care Finance Administration is that they make no precipitous decisions to meet congressional deadlines as far as getting a system up and running, that might preclude the further development of ways in which you can have a system detect inappropriate drug regimens or conflicting ones.

I think we just have to also mention that the elderly, in large respect, have peculiar habitat patterns, that they, among our population, tend to live in different parts of the country during the course of the same year, the so-called "snow birds" going from the northeast down to Florida or into the Sun Belt. That means that oftentimes the elderly will have physicians in their home area as well as in the Sun Belt area and the physicians oftentimes do not consult or are not aware of what drug regimens are being provided in the other area; consequently, you have interactions that are bad for the patients.

I think this new system that is being set up and financed by the Federal Government affords us an opportunity that we cannot miss. Therefore, we urge very, very heavily the Health Care Finance Administration to make no decisions about the automation process that would forestall or preclude some real good drug utilization review efforts using the computer, because I think it's very unlikely and unreasonable to expect that pharmacists, with the millions and millions of prescriptions that are being issued each day, that they can be expected to have drug counseling on each prescription. The computerization I think would help us along that line.

We also have to mention the patient. We found there is a large problem of noncompliance by the elderly patient with their drug regimens, even when they have warning labels, even when they have instructions, even when they have counseling, that they don't follow the advice of their physician or the pharmacist. As I say, that is such an important part of this problem that we feel we need to have a separate study trying to understand why that is the case and try to see if we can come up with some ideas as to how we can help along that line, to make sure that the elderly are going to follow the instructions that are given by their health care professionals.

The medication problems that the elderly have include not only underutilization, where they will not follow the instructions and use less than what they're told they should use, but they also overuse it, or they fail to follow the schedule, or they may feel they should share with the family the drugs that they get, the spouse, or maybe they should use some other members of the family, daughter or son, grandson, with a drug to help them with a problem and they medicate themselves. The fact is, over half of the elderly do not comply with their daily drug regimens. That is a very serious problem.

Again, one of the things that is really making this a growing problem is the fact that our population is getting older. The fact is we're getting older but not necessarily healthier, and that this elderly population of 65 and older currently represents only 12 percent of our population, and yet they use 30 percent of the prescribed drugs. They average a much higher number of prescriptions per year than any other part of our society—15.5 prescriptions per year per elderly individual. This means they use them more; they have different drugs, and they are more likely to have problems as a result of it.

In addition, elderly people account for 39 percent of all hospitalizations and half the deaths from drug reactions. In 1987, Medicare paid more than $500 million for more than 200,000 hospitalizations which were related to adverse drug reactions and overdoses. Now, this is a gross understatement. We obtained this information by looking at the V codes that Medicare maintains in their statistical samples, what they use for all kinds of different projections. It does not include where the codes do not reflect the fact it was drug mismedication, but the underlying disease was identified.

The fact is, we have tested some of that data and we find that may be understated as much as 50 or 70 percent. So the number is much higher than that. But what it does tell us, regardless of what number we wish to chose, it is a very large number and it costs the taxpayers an awful lot, as well as having an adverse effect on the elderly community.

In our report, which as I mentioned, Mr. Chairman, we will relate to the committee in final form, we recommended that HCFA should begin development of a comprehensive DUR program designed to promote quality care, control program costs, and ensure program integrity.

We also recommended that HCFA and the Public Health Service should promote improvements in the prescribing, dispensing and utilization of drugs for older adults by, one, making funding available to finance research and demonstration projects that will test drug intervention review interventions and evaluate their relative benefits and costs; secondly, expedite the issuance of final FDA guidelines, which we alluded to before, to manufacturers to ensure there is adequate testing of drugs before being approved for marketing by the Health Care Finance Administration for payment.

We recognize the HCFA and FDA have already began taking these steps toward implementation of many of these recommendations, and we're very pleased about that.

The last point I would make, Mr. Chairman, is that we are, indeed, working on a large number of other studies. This global study, I am pleased to report—and you won't often find the Inspector General pleased to report on this—really drew a lot of comments. The reason for that is because this was not a traditional audit-type report. As a result of that, we not only asked for comments from the Department, FDA, the Public Health Service, the Health Care Finance Administration, but we also went out to the American Medical Association, the National Association of Boards of Pharmacy, the American College of Pharmacy, the Public Citizens Health Research Group—we even went to the Pharmaceutical Manufacturers Association and the National Association of Chain Drug Stores—because what we wanted, and I'm sure the reason why you're having this hearing, is we wanted everybody's viewpoint laid on the table, we wanted people to, in fact, sit down and look at this issue from a global standpoint in order to have a better understanding.

As a result of the comments we got back from all these sources, our report, from the draft to the final, has doubled in size, because we have incorporated an enormous amount of new information. We have responded to a lot of suggestions in a very positive fashion. What we really want, as a final product to this committee, and to the American taxpayers and beneficiary community, is a good benchmark; where are we today, where should we be going tomorrow. We are very pleased that this report is now beginning to take shape along that line.

[See appendix 1, p 216 for the report entitled, "Medicare Drug Utilization Review" submitted by Mr. Kusserow]

Mr. KASSEROW. With that, Mr. Chairman, let me stop and devote the rest of the time to answering questions and concerns that you might have.

[The prepared statement of Richard P. Kusserow follows:]

TESTIMONY

OF

INSPECTOR GENERAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SELECT COMMITTEE ON AGING

SUBCOMMITTEE ON HUMAN SERVICES

ON

IMPLEMENTATION OF THE DRUG PROVISIONS:

MEDICARE CATASTROPHIC COVERAGE ACT

APRIL 19, 1989

GOOD MORNING, MR. CHAIRMAN AND MEMBERS OF THE SUBCOMMITTEE. I AM RICHARD KUSSEROW, INSPECTOR GENERAL FOR THE DEPARTMENT OF HEALTH AND HUMAN SERVICES. I AM HERE THIS MORNING AT YOUR REQUEST TO SHARE WITH YOU THE RESULT OF OUR RECENT STUDY ON DRUG UTILIZATION REVIEW. BEFORE ELABORATING ON THE FINDINGS OF OUR STUDY, I WOULD LIKE TO PROVIDE YOU WITH SOME BACKGROUND ON THIS ISSUE AND THE EXTENT OF OUR INVOLVEMENT IN THIS AREA.

BACKGROUND

IN JULY 1988, CONGRESS PASSED THE MEDICARE CATASTROPHIC COVERAGE ACT WHICH, IN PART, MANDATED A PRESCRIPTION DRUG BENEFIT FOR MEDICARE BENEFICIARIES. THIS MANDATE OFFERS THE DEPARTMENT A SIGNIFICANT OPPORTUNITY TO DESIGN AND OPERATE A MULTI-LEVEL DRUG UTILIZATION REVIEW (DUR) EFFORT TO IMPROVE QUALITY OF CARE, AVOID UNNECESSARY MEDICARE AND PERSONAL EXPENDITURES AND MAINTAIN PROGRAM INTEGRITY.

FOR YOUR INFORMATION, A DRUG UTILIZATION REVIEW, OR DUR IS A FORMAL PROGRAM FOR ASSESSING DATA ON DRUG USE AGAINST EXPLICIT, PROSPECTIVE STANDARDS, AND, AS NECESSARY, INTRODUCING REMEDIAL STRATEGIES TO ACHIEVE SOME DESIRED END. THE THREE PRIMARY OBJECTIVES ARE:

(1) IMPROVEMENT IN THE QUALITY OF CARE;

(2) CONSERVING PROGRAM FUNDS AND INDIVIDUAL EXPENDITURES; AND

(3) MAINTAINING PROGRAM INTEGRITY, I.E., CONTROLLING PROBLEMS OF FRAUD AND BENEFIT ABUSE.

IN ANTICIPATION THAT FINAL LAW WOULD INCLUDE A PRESCRIPTION DRUG BENEFIT PROVISION, OUR OFFICE INITIATED A STUDY IN FEBRUARY 1988 TO IDENTIFY THE MAJOR POLICY AND PROGRAM ISSUES

RELEVANT TO THE DEVELOPMENT OF A MEDICARE DUR STRATEGY. DATA FOR THIS INSPECTION WAS GATHERED FROM THREE MAJOR SOURCES:

- A SURVEY OF 48 STATE AGENCIES THAT HAVE BEEN PROVIDING PRESCRIPTION DRUG BENEFITS TO MEDICAID PATIENTS AND OPERATING THEIR OWN DUR PROGRAMS AS WELL AS AN ADDITIONAL 6 STATE AGENCIES THAT PROVIDE SIMILAR BENEFITS THROUGH PR[illegible]GNED SPECIFICALLY FOR THE ELDERLY.

- A REVIEW OF RELEVANT RESEARCH FINDINGS RELATED TO DRUG UTILIZATION AMONG THE ELDERLY, INCLUDING TOPICS SUCH AS OVERALL UTILIZATION PATTERNS, PROBLEMS OF MISMEDICATION AND EXPERIMENTAL INTERVENTIONS TO IMPROVE DRUG USE.

- A SERIES OF INTERVIEWS WITH RESEARCHERS, ACADEMICS AND PRACTITIONERS IN THE FIELDS OF GERIATRICS AND

PHARMACOLOGY; FORMER AND CURRENT POLICY MAKERS AT THE STATE AND FEDERAL LEVELS; CONGRESSIONAL STAFF INVOLVED IN DRAFTING THE ACT; AND PRIVATE SECTOR PHARMACEUTICAL PROVIDERS.

OUR OVERALL AIM OF THIS INSPECTION WAS TO FOSTER THE DEVELOPMENT AND IMPLEMENTATION OF AN EFFECTIVE DUR SYSTEM UNDER THE MEDICARE PROGRAM. TOWARD THIS END, WE SOUGHT TO PROMOTE A BETTER UNDERSTANDING OF THE MAJOR PROBLEMS AND NEEDS THAT A DUR PROGRAM SHOULD ADDRESS AND OF THE RELEVANT INSIGHTS THAT EMERGE FROM RESEARCH AND EXPERIENCE.

FINDINGS

THE REPORT, WHICH WE EXPECT TO COMPLETE SHORTLY, REPRESENTS INFORMATION AND RECOMMENDATIONS THAT WE HOPE WILL HELP THE DEPARTMENT TAKE MAXIMUM ADVANTAGE OF THE OPPORTUNITY TO DESIGN AND IMPLEMENT A MULTI-FACETED DUR PROGRAM. THE FINDINGS

ATTEMPT TO DESCRIBE THE WIDESPREAD PATTERN OF MISMEDICATION AMONG OLDER ADULTS, IDENTIFY THOSE ASPECTS OF THE DRUG THERAPY DELIVERY SYSTEM THAT HAVE CREATED THE PROBLEM, AND DESCRIBE DUR INTERVENTIONS THAT APPEAR MOST PROMISING.

MISMEDICATION AMONG THE ELDERLY IS FREQUENTLY REFERRED TO AS THE OTHER DRUG PROBLEM IN THE UNITED STATES. IN OUR REVIEW, WE FOUND THAT THERE IS A WIDESPREAD PROBLEM OF MISMEDICATION AMONG OLDER ADULTS. IN ADDITION, WITH THE IMPLEMENTATION OF THE MEDICARE PRESCRIPTION DRUG BENEFIT, THE UTILIZATION OF DRUGS, AMONG THE ELDERLY MAY RISE. THIS COULD CAUSE AN INCREASE IN MISMEDICATION UNLESS AN EFFECTIVE DUR PROGRAM IS DEVELOPED. AMERICANS 65 YEARS AND OVER CURRENTLY REPRESENT ONLY 12 PERCENT OF THE POPULATION YET THEY USE 30 PERCENT OF THE PRESCRIBED DRUGS AND THEY AVERAGE 15.5 PRESCRIPTIONS PER YEAR.

IN ADDITION, ELDERLY PERSONS ACCOUNT FOR 39 PERCENT OF ALL HOSPITALIZATIONS AND HALF OF THE DEATHS FROM DRUG REACTIONS. WE HAVE EXAMINED A 1 PERCENT SAMPLE OF ALL MEDICARE DISCHARGES FOR 1987 AND FOUND THAT IN 1987, THE MEDICARE PROGRAM PAID MORE THAN $500 MILLION FOR MORE THAN 200,000 HOSPITAL ADMISSIONS WHICH WERE RELATED TO AN ADVERSE DRUG REACTION OR OVERDOSE, WHICH OCCURRED EITHER BEFORE ADMISSION OR DURING THE HOSPITAL STAY. MOREOVER, BECAUSE HOSPITALS DO NOT ALWAYS CODE THESE DRUGS REACTIONS AND OVERDOSES, THESE MEDICARE FIGURES MAY SIGNIFICANTLY UNDERSTATE THE MAGNITUDE OF THE PROBLEM. WE ARE DOING FURTHER WORK TO DETERMINE THE EXTENT OF THE PROBLEM OF HOSPITALS NOT CODING CASES INVOLVING MISMEDICATION.

MISMEDICATION MAY OCCUR IN FOUR WAYS:

-- HIGHER DOSES ARE PRESCRIBED IN CASES WHEN A LOWER DOSE WOULD PROVIDE THE SAME BENEFITS WITH LOWER RISKS.

-- DRUGS WITH A GREATER POTENTIAL FOR ADVERSE REACTIONS ARE PRESCRIBED WHEN A LESS DANGEROUS DRUG WOULD BE JUST AS EFFECTIVE.

-- THE PARTICULAR DRUG PRESCRIBED IS UNNECESSARY EITHER BECAUSE THE PATIENT'S CONDITION HAS BEEN MISDIAGNOSED OR BECAUSE NONDRUG THERAPY COULD BE SUBSTITUTED.

-- THE COMBINATION OF THE PRESCRIBED DRUG WITH OTHER DRUGS IN THE PATIENT'S REGIMEN PRODUCES ADVERSE EFFECTS.

SECONDLY, WE FOUND THAT THE PROBLEM WITH MISMEDICATION AMONG THE ELDERLY REFLECTS A SERIES OF SYSTEMIC WEAKNESSES THROUGHOUT THE DRUG THERAPY DELIVERY SYSTEM. BASED ON OUR RESEARCH AND ANALYSES, WE BELIEVE THAT SIGNIFICANT IMPROVEMENTS ARE NECESSARY AT VARIOUS LEVELS OF THE DELIVERY SYSTEM TO

SIGNIFICANTLY REDUCE THIS MEDICATION PROBLEM.

AT THE MANUFACTURES LEVEL, SOME PROGRESS HAS BEEN MADE. THE FDA AND THE MANUFACTURERS REPORT THAT DRUG COMPANIES ARE MORE OFTEN INCLUDING THE ELDERLY IN CLINICAL TRIALS AND ARE MORE OFTEN PROVIDING GERIATRIC LABELING INFORMATION ON DRUGS COMMONLY USED BY THE ELDERLY. BUT CONTINUED PROGRESS MUST BE MADE, BOTH WITH RESPECT TO THE TESTS DONE PRIOR TO FDA APPROVAL OF A DRUG AND THE POSTMARKETING EXPERIENCE OF DRUGS HEAVILY USED BY THE ELDERLY.

AT THE PHYSICIAN LEVEL, WE FOUND THAT THERE IS INADEQUATE TRAINING AND EDUCATION FOR PHYSICIANS IN THE AREA OF GERIATRIC PHARMACOLOGY, LEADING TO PRESCRIBING PATTERNS THAT ARE SUBOPTIMAL FOR OLDER ADULTS. SOME PHYSICIANS RELY ON THE REPRESENTATIVES OF DRUG MANUFACTURERS AS THEIR PRIMARY SOURCE OF INFORMATION ON THESE DRUGS, WHILE OTHER PHYSICIANS ENGAGE IN

THEIR OWN INDEPENDENT LITERATURE REVIEW AND ADDITIONAL COURSE WORK WHICH ENABLE THEM TO MAKE INDEPENDENT DETERMINATIONS ON THE EFFECTIVENESS OF MEDICATIONS. IN BOTH SITUATIONS, HOWEVER, WORK MAY STILL BE INSUFFICIENT TO MEET THE NEEDS OF THE GROWING ELDERLY POPULATION. AS A RESULT, WE ARE SUPPORTIVE OF IMPROVEMENTS IN PROGRAMS WHICH PROVIDE MORE PHYSICIANS WITH MORE INFORMATION ON ISSUES PERTAINING TO GERIATRIC PHARMACOLOGY.

AT THE COMMUNITY PHARMACY LEVEL, WE FOUND THAT ONLY A SMALL PERCENTAGE OF ELDERLY PATIENTS RECEIVE DRUG COUNSELING EVEN WHEN THOSE SERVICES ARE MANDATED BY STATE REGULATION. THIS PROBLEM IS FURTHER COMPLICATED BY THE FACT THAT MANY PHARMACISTS DO NOT PERFORM ADEQUATE REVIEWS OF PATIENTS' DRUG REGIMENS OR CONSULT WITH PHYSICIANS AND PATIENTS WHEN POTENTIAL PROBLEMS OF CONFLICTING DRUGS ARE IDENTIFIED.

IN OUR REPORT, WE EXPRESSED OUR SUPPORT FOR PROVIDING PHARMACISTS WITH DETAILED INFORMATION, AS PART OF THE MEDICARE DRUG UTILIZATION REVIEW PROGRAM, ON THE DRUG REGIMEN OF THE PATIENT. WE BELIEVE THAT THIS INFORMATION WILL ASSIST PHARMACISTS IN PROVIDING BETTER DRUG COUNSELING. WE CONSIDER THIS TO BE AN IMPORTANT LONG TERM GOAL OF THE DEPARTMENT IN STRUCTURING THE DRUG UTILIZATION REVIEW PROGRAM. WE BELIEVE THAT IT CAN BE GRADUALLY ADDED AS A COMPONENT OF OR ADJUNCT TO THE ELECTRONIC CLAIMS PROCESSING SYSTEM WHICH THE HEALTH CARE FINANCING ADMINISTRATION (HCFA) IS NOW DEVELOPING, WITHOUT INTERFERING WITH THE ESTABLISHMENT OF THIS IMPORTANT NEW SYSTEM. CONVERSELY, WE BELIEVE THAT NO ACTIONS SHOULD BE TAKEN NOW WHICH WOULD PREVENT THE ESTABLISHMENT OF THE EFFECTIVE DUR SYSTEMS IN THE FUTURE. OF COURSE, THIS SYSTEM MUST CONTAIN APPROPRIATE SAFEGUARDS TO INSURE THE CONFIDENTIALITY OF THE PATIENT DRUG RECORDS. THE PRIVACY RIGHTS OF INDIVIDUALS IS PROTECTED THROUGH VARIOUS STATE LAWS AND PROFESSIONAL PRACTICE

STANDARDS AS WELL AS FEDERAL LAW. THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, THROUGH HCFA, IS DEVELOPING STANDARDS FOR THE COLLECTION AND MANAGEMENT OF DATA THAT ARE CONSISTENT WITH THESE STATUTORY REQUIREMENTS AS ESPOUSED IN THE CATASTROPHIC COVERAGE ACT OF 1988.

FINALLY, AT THE PATIENT LEVEL, WE CONTINUE TO SEE A LARGE PROBLEM OF NONCOMPLIANCE BY ELDERLY PATIENTS WITH THEIR DRUG REGIMENS. THESE MEDICATION PROBLEMS INCLUDE UNDERUTILIZATION AND OVERUSE OF DRUGS, SHARING WITH FAMILY AND FRIENDS, AND USE OF DAMAGED MEDICATIONS.

THE HEALTH CARE FINANCING ADMINISTRATION AND MEDICAID STATE AGENCIES HAVE DESIGNED DRUG UTILIZATION REVIEW PROGRAMS TO OVERSEE THEIR MEDICAID DRUG BENEFITS. THESE SYSTEMS AND THE WORK OF CERTAIN RESEARCHERS PROVIDE VALUABLE GUIDANCE TO THOSE CHARGED WITH DESIGNING THE DEPARTMENT'S MEDICARE DRUG

UTILIZATION REVIEW PROGRAM.

RECOMMENDATIONS

TO CORRECT THE PROBLEMS FOUND IN OUR STUDY, WE HAVE DEVELOPED THE FOLLOWING RECOMMENDATIONS. FIRST, WE BELIEVE THAT THE HEALTH CARE FINANCING ADMINISTRATION SHOULD BEGIN THE DEVELOPMENT OF A COMPREHENSIVE DRUG UTILIZATION REVIEW PROGRAM DESIGNED TO PROMOTE QUALITY OF CARE, CONTROL PROGRAM COSTS AND ENSURE PROGRAM INTEGRITY. THE DRUG UTILIZATION REVIEW PROGRAM PROCESS SHOULD ENCOMPASS ALL BENEFICIARIES, NOTWITHSTANDING DEDUCTIBLE STATUS.

SPECIFICALLY, WE BELIEVE THAT THE HEALTH CARE FINANCING ADMINISTRATION SHOULD:

-- UTILIZE PREPAYMENT EDITS TO IDENTIFY CASES OF DUPLICATE AND ERRONEOUS BILLING AND PERFORM OTHER PROGRAM

INTEGRITY AUDIT FUNCTIONS ON A RETROSPECTIVE BASIS TO IDENTIFY CASES OF FRAUD AND ABUSE.

-- EVALUATE THE QUALITY OF INFORMATION SUPPLIED BY THE FISCAL INTERMEDIARY TO PHARMACISTS AND ASSESS THE RANGE AND NATURE OF USE OF THAT INFORMATION BY PHARMACISTS.

-- CONDUCT SOME AUTOMATED THERAPEUTIC REVIEW.

-- UNDERTAKE POSTPAYMENT REVIEWS TO DETECT PATTERNS OF MISMEDICATION AND TAKE APPROPRIATE ACTIONS TO PREVENT RECURRENCES.

-- PROVIDE EFFECTIVE EDUCATION TECHNIQUES FOR HEALTH CARE PROFESSIONALS AND PATIENTS (AS DESCRIBED IN THIS REPORT).

IN ADDITION, WE HAVE STRONGLY RECOMMENDED THAT THE HEALTH CARE FINANCING ADMINISTRATION AND THE PUBLIC HEALTH SERVICE, INDIVIDUALLY AND COLLABORATIVELY, SHOULD PROMOTE IMPROVEMENTS IN THE PRESCRIBING, DISPENSING, AND UTILIZATION OF DRUGS FOR OLDER ADULTS BY TAKING THE FOLLOWING ACTIONS:

- MAKE FUNDING AVAILABLE TO FINANCE RESEARCH AND DEMONSTRATION PROJECTS THAT WILL TEST DRUG UTILIZATION REVIEW INTERVENTIONS AND EVALUATE THEIR RELATIVE BENEFITS AND COST.

- ESTABLISH A BLUE RIBBON PANEL TO DEVELOP DRUG UTILIZATION REVIEW CRITERIA THAT WILL SERVE AS A NATIONAL STANDARD FOR DRUG UTILIZATION REVIEW PROGRAM CONDUCTED THROUGHOUT THE COUNTRY.

- -- EXPEDITE THE ISSUANCE OF THE FINAL FOOD AND DRUG ADMINISTRATION GUIDELINES TO MANUFACTURERS TO ENSURE ADEQUATE TESTING OF DRUGS ON ELDERLY POPULATIONS. THESE WOULD SUPPLEMENT THE GUIDELINES ISSUED BY FDA IN 1988 THAT CALL FOR DRUG SPONSORS TO ANALYZE THE INFLUENCE OF AGE ON THE RESULTS OF CLINICAL TRIALS.

WE ARE CONTINUING TO WORK ON A NUMBER OF STUDIES RELATED TO THE PROBLEMS OF MISMEDICATION AMONG THE ELDERLY AND THE NEED FOR FEDERAL OVERSIGHT SYSTEMS. SPECIFICALLY, WE ARE STUDYING STATE PHARMACY BOARDS, COMMUNITY PHARMACY COUNSELING, MEDICATION REGIMENS, PRIVACY PROTECTION AND ENFORCEMENT OF DRUG REGULATIONS.

THIS CONCLUDES MY PREPARED REMARKS. I WOULD BE HAPPY TO ANSWER ANY QUESTIONS YOU MAY HAVE.

Mr. Downey. Mr. Kusserow, let me first congratulate you and your staff for this excellent report. I think it really pleases us to know that there are people in the bureaucracy who are working as hard and in as dedicated a way as you are.

You started to, at the end of your remarks, characterize the reaction to your report. Is there any other reaction to the draft report that surprised you?

Mr. Kusserow. The biggest surprise that we had is that we had so many favorable comments. IG's don't usually get favorable comments on their reports. We did get a very strong expression of support from a wide variety of people that we have asked for comments. Even those that reacted in a negative fashion did so, fortunately, with constructive criticism. They say, "Why don't you look at this, or why don't you take into consideration that." So we did also have strong criticism.

But the end result of that process is that now we have a report that I think will incorporate all the various viewpoints. We have included the negative comments as well as the positive comments. Many of the positive comments we just incorporated in the body of the report and accepted, and where we have disagreed we have so indicated in our appendices. So what the committee will have is probably a very good companion piece to this hearing. You're going to hear a lot of the same things.

I am very pleased—In fact, I took the liberty this morning to look over a lot of the statements that were submitted for the record, and I am very pleased to note that virtually all the statements are now very much consonant with the major thrust of our report. I can say conversely that our report really reflects a lot of what's in the statements. So from that standpoint, if one of the purposes of this committee was to begin to develop a consensus as to where we are, I think that, indeed, we are getting to that objective very quickly.

Mr. Downey. In your report you say—and I'm quoting—"drug companies typically perform clinical studies required to secure FDA approval on healthy young adults, even though the product may ultimately be approved and marketed for a condition that is common among the elderly." Yet we observe in numerous presentations that will be made in testimony today, and the FDA will be saying, that drug companies are increasingly using older people in their tests.

How do you resolve this?

Mr. Kusserow. I don't think it's difficult. I think the difference is we're taking a snapshot. One of the criticisms we had, and I thought was constructive, was to say you need to recognize more what we're doing in terms of making progress. We are improving in this area.

The concerns that I have, in fact, are the your next witness, in full regalia, is the Commissioner of FDA—this is uniform day in the Public Health Service, so he's here in full admiral's uniform. I think you will see he is also going to reflect on the fact that there are still areas where we need improvement.

One of the areas is that, though we have a pretty good understanding of the elderly up to maybe when they're 70 years of age, they clearly are a different group than the geriatrics over 70 years of age. In fact, I think we need to have a better understanding that when you get into a geriatric state, your conditions change. When you're 65 or 70, you're not going to be the same as when you're 85 or 90. I think we can learn more about the discrete differences in the elderly. The elderly is too broad a category.

As a matter of fact, one of the things I found very frustrating, as we were doing literature searches in the preparation of this particular report, was the fact that people defined elderly differently. Some say the elderly are 60 and older; some say 65 and older; some say it's 55 and older. Some say it's when you become an octogenarian. The fact is that when you talk about the elderly, you're talking about a very large band of people and in a very broad age expanse. I think what we're suggesting is that a lot more can be done in this area.

We recognize there is enormous progress. We're pleased about it. But I don't think you could find a witness today that would say they are going to be pleased to stop where they are, that we have no need to go further. In fact, that might be a good question. I don't think you're going to have anybody who is going to say that we have done everything we need to do.

The fact of the matter is, so long as our population is getting older, so long as we're having people move through the years and getting into the geriatric arena, we're going to have to know more about the most advanced age of our population.

One of the things that in looking at Medicare I found, which I though was extraordinarily interesting, was that half the Medicare expenses are really in dealing with people in their last year of life, actually the last 6 months of life. We need to know more about people at the upper limits of their life. I don't think you're going to find anybody who is going to say we know enough about that.

Mr. Downey. Dr. Young also says in his testimony that there is—and this is quoting from what has been submitted to the committee—"there is little scientific evidence that the elderly have, as a general matter, more reactions than other individuals when the number of medications used is taken into account."

Now, that appears to conflict a little bit with your report.

Mr. Kusserow. No, not really.

Mr. Downey. Would you elaborate?

Mr. Kusserow. Yes. The point I'm making—and I don't think we disagree on this point. What I'm suggesting is not because you're getting older that you have a mismedication problem necessarily. What I'm saying is that when you get older, you have a larger number of prescriptions, per patient, per year. The controlling factor seems to be not age so much as the number of prescriptions. You could be younger. The more prescriptions you have, the greater the likelihood for mismedication. So it is not inconsistent. One is talking about apples and one's talking about pears here. What we saying is, as you get older, you have a higher number of prescriptions. The greater number of prescriptions you have, the greater the likelihood of mismedication. So I think that's how you resolve the difference between the two.

Mr. Mangano. There is one other thing to add to that, and that is that there's a secondary factor going on here, and that is the aging process itself, which changes the physiology of the person, including a decrease in the functioning of the kidneys and other organs of the body. So it's a combination of both. It's the added increases in the number of drugs as well as the physiological changes in the body.

Mr. KUSSEROW. And, of course, where you're really looking there—talking about again the same population I alluded to before—that is, not just the elderly as described between 65 and 70, but people who are over 70 that are really in a geriatric stage of life. In fact, as I scanned through Dr. Young's testimony this morning, I think he is going to be speaking to that population group. I think that is a variable that will deduce, I suspect, that there is a difference.

Mr. DOWNEY. I am certainly not a scientist nor a physician, but is there any way, from your perspective—and I will ask this of Dr. Young—that in preparing a clinical trial, one can control for the factors of additional drug use? Is that done?

Mr. KUSSEROW. I'll let Dr. Young answer that question. You gave me an out for that one and I'll take it. I'll let him answer it.

Mr. DOWNEY. A good answer, I suppose.

You also indicate that the office is in the process of doing additional studies, and you alluded to some. I am particularly interested in the community pharmacy counseling study and the private protection study.

Could you elaborate on those two, briefly?

Mr. KUSSEROW. What we're trying to understand is—we recognize there's a lot of different control points all along. We're concerned about how they go about developing drugs that will eventually be used in connection with dealing with the elderly. We're concerned also about the physicians. But we're also concerned about the pharmacists. We do know that that is our best chance of detecting mismedication.

There is also the area where Medicare is going to be putting a lot of effort in response to the catastrophic health insurance legislation. What we want to know is more about why there isn't more drug counseling going on, and yet, and the same time, we want to find out where there is drug counseling going on.

The fact of the matter is, one of the things we have observed—and you can't help but observe if you watch television—you get commercials on many chain drug stores that really promote the fact that they have controls within their computerized database to alert the patient, alert the pharmacist and the patient, to mismedication potential problems. We want to understand far more what's going on in that arena: what are the best practices out there; where are we using this rising technology to advantage in giving guidance to the patient community, particularly the elderly patient community. We think, as a result of this study, we should come back with probably a pretty good understanding of what's good is out there, what's bad that's out there, and how can we make the bad good. That's sort of a thumb-nail sketch of what our objectives are.

Mr. DOWNEY. Lastly, in your cover letter to Dr. Roper of HCFA, you said that the congressional mandate to establish a Medicare DUR program presents a significant opportunity to design and operate a multilevel system to improve quality of care, avoid unnecessary Medicare and personal expenditures, and maintain program integrity. You also alluded in your statement, I think, to guidelines that we had given them for setting the system up. You are warning us, and him, I think, that we shouldn't be arbitrary in this regard.

Mr. KUSSEROW. Well, I think what we're trying to do is wave a cautionary flag, saying we are moving ahead very quickly to implement an automated system to meet the requirements of the catastrophic health insurance legislation. What is unclear and where there's some ambiguity is precisely what did Congress intend to be included in drug utilization review. It is our position—and I find this very peculiar, because normally you look at the Inspector General and you would see a green eye shade, garters on the sleeve, talking about dollars and cents. You would think I would be sympathetic to the fact that you want payment safeguards in there, to make sure Uncle Sam isn't going to lose any money on this thing and we don't have overutilization because we pay for it.

My concern is not on that side so much. My concern is that, as we rush ahead to build that kind of a system, we do not forget the fact that there are other things you can build into a computerized database that will have quality of care implications, that, in fact, will act as a control point to prevent mismedication. I think, quite frankly, given the two initiatives, I am almost more concerned about the secondary one than I am the primary one. I think there's a real opportunity here to get at a problem that is very serious—mismedication among the elderly.

Now, maybe I can be cavalier about that and say I don't care what the costs are along that line, of building that kind of system. But I will say I recognize that if, in fact, you reduce the amount of mismedication problems among the elderly, it's going to save the system in the long run because it's going to mean fewer hospitalizations for prescription drug-related problems. So I just don't want the Health Care Finance Administration to forget the fact that there's a real opportunity here to do drug utilization review for quality of care purposes in addition to fiscal care purposes.

Mr. DOWNEY. Are you optimistic that they've been listening to your flag waving and admonition?

Mr. KUSSEROW. I can assure you that they've been listening to what we've been saying. The question is whether we have convinced them sufficiently. I think, quite frankly, they are very sympathetic to that and I think they really want to do that. I think they're concerned, quite frankly, more than anything else, that Congress put an arbitrary date down saying you will have by such and such a date, and they're trying to race ahead to meet that congressional mandated deadline. To have the Inspector General come along and say as you're doing this, don't forget to make sure you have these other things plugged into the system so that you can also do these other things, and they say wait a minute, that's going to slow us down and we're scared that we're not going to be able to meet this deadline. So I felt that, as you pointed out, I should wave that cautionary flag not only to the Health Care Finance Administration but to the Congress and say be careful because decisions are going to be made that are going to bind us for the future; what are those decisions that you want to have made.

Mr. DOWNEY. I will transmit what you've said to Congressman Stark, who is my colleague on the Ways and Means Committee who has jurisdiction over this. I'm not sure whether he may be completely up to speed, but we appreciate that point.

I agree with you. I think we have to be concerned about cost. But as you have estimated, the cost is anywhere from $500 million to a billion for people showing up in hospitals as a result of the misapplication or misuse of prescriptions; there is much to be saved if we do it properly to begin with.

Thank you, Mr. Kusserow. Ms. Snowe?

Ms. SNOWE. Thank you, Mr. Chairman.

To follow up on that question, Mr. Kusserow, do you think that 2 years is an adequate amount of time in which to develop a comprehensive drug utilization review system?

Mr. KUSSEROW. I think it's extremely optimistic. I will tell you that the Health Care Finance Administration is doing its best to meet that deadline. I think that, in fact, Congress may want to review that and decide whether you want to hold a hard and fast deadline to it. But before you can do that, I think Congress has to really tell the Health Care Finance Administration, very clearly and specifically, without ambiguity, exactly what it expects to come out of that system.

Ms. SNOWE. I noticed in your original report that you issued in January, you mentioned on page 26 of that report that ". . . a critical error will be made if substantial attention is not given to the design and development of a comprehensive DUR program to be implemented when the drug benefit becomes effective." And yet in your statement, you indicated that, as far as the drug regimen of a particular individual is concerned, that would be more of a long-term goal of the program rather than an immediate goal or one that is in place when the program becomes effective.

The conferees of the Medicare catastrophic legislation indicated that, in fact, they expected that to be on line when the review program was put in place.

Mr. KUSSEROW. What I had suggested, and what I continue to suggest as perhaps a way in which we can have everybody's goals met, is to look upon this as a two-phased kind of effort. The first phase is to get the payment system up. But what I would not like to see is any decisions being made in the first phase that would preclude going to the second phase, which is to have a much more comprehensive drug review system. That's how I make it consistent. If, indeed, they must meet this deadline, and if they feel they cannot meet that deadline, if they're trying to put all the extra whistles and bells on it that would deal with the mismedication problems, then at least what they should do is design a system that would allow it to easily adapt to the second phase, which would provide that.

Ms. SNOWE. So in 1991, for example, when this review program is in place, it will not be a prospective system; it would only be evaluating the prescriptions that have been prescribed in the past and evaluating them based on—

Mr. KUSSEROW. It would be much more limited than what we would like to see.

Ms. Snowe. Then that is somewhat contrary to the intent of Congress, and perhaps it's something that we need to review.

Mr. Kusserow. Well, you have a deadline; you have the art of the possible. What can you do within the constraints of the deadline. If, in fact, the deadline is to be met, I don't see how they can do all the things that we would like to see them do within the time constraints. However, what I do not want them to do is make decisions that would preclude them from going to the second phase—that is, building on to that system the other kinds of quality review that we think is imperative to meet the intent of the Congress.

Ms. Snowe. So the first phase would essentially be a claims processing review of payments already made under Medicare?

Mr. Kusserow. If that is the way that Medicare says they must proceed in order to meet the deadline, that would be the case. I just do not want them to build a system that then would preclude going to a follow up on that, and that is, adding these other components to that.

They are basically saying it is hard to build a 747 without building a Wright Brothers type of aircraft first. I say fine, but don't do anything in designing that first aircraft—a bare minimum to me—do not design something that could not be adapted into an evolving stage to provide a much more comprehensive drug utilization review process than just the payment system.

Ms. Snowe. I think your report outlined very well the solutions necessary to address this problem. What can be done now in the more immediate and critical stage—and your report did address that—concerning the very few drugs which are commonly used by the elderly which should provide specific instructions for the elderly.

It seems to me that one of the issues we are going to try to address here today and with our next witness is, of course, the whole issue of clinical testing and studies and the use of elderly in those studies. Why at this point do you believe the Food and Drug Administration has not issued those guidelines since 1983?

Mr. Kusserow. I think the simple answer is that it's an extremely complex process. Woe be unto me to say this, but that involves a lot of bureaucratic effort that is very difficult in Government to get out. So I think a lot of it is the complexity and the bureaucracy. I just think we have to put that on the front burner and move very aggressively toward getting them out.

Although I admit freely that I can see that enormous progress is being made, it just seems to me that we need to get to that plateau where we get those final guidelines out and we start getting more specific types of data instructions in to have a better understanding as to what's going on. I think we need to get to that plateau. When we get to that plateau, progress is made.

But I would consider that just one plateau. We wouldn't stop there. I think we need to continue to work in this arena. It is too big a problem area and there are too many other things that need to be done. But at least that is a very significant plateau to get to, and I would urge very strongly that we get there as soon as possible, and I hope Dr. Young can give you some good insight as to when that's going to be.

Ms. SNOWE. I would agree with you, because it seems to me that is at least something that can be done now and would have some impact on this entire issue.

Mr. KUSSEROW. I don't think the industry really needs that. I think yes, it's good that the industry is moving on its own, and yes, it has a general guideline has to which way to go and how to alert. But I think more specific guidance is necessary and one that is statistically more reliable than what we have now.

Ms. SNOWE. Right. And don't you think uniformity is important in terms of the standards that drug manufacturers use, and although some of them are using elderly in their clinical test studies, there is not a uniformity of standards by which they evaluate these studies.

Mr. KUSSEROW. That's precisely the difference, yes.

Ms. SNOWE. And do you think uniformity then is critical?

Mr. KUSSEROW. I think it is very critical, yes.

Ms. SNOWE. I don't have any further questions. I just want to congratulate you on your study and for moving and advancing this issue to the forefront.

Mr. KUSSEROW. Thank you very much.

Mr. DOWNEY. Mr. Duncan.

Mr. DUNCAN. Mr. Kusserow, I'm not sure I'm clear. How much of this is a problem of mismedication as opposed to a problem of misuse or abuse of these drugs?

Mr. KUSSEROW. Well, I hope that, when I'm able to come back to you and report some of the results of our other studies, I can give you a more exact answer. I think that a very large part of the problem is the fact that, for whatever reason, the elderly do not follow instructions. Now, why is that the case? I think a very large part of it is that they're not properly counseled by their pharmacists and improperly counseled by their physician.

We do know from other studies we have done with the elderly that they rely far more upon face-to-face advice than they do upon the written instructions. For some reason, as people get older, they become more suspicious of the written instructions and rely more upon the assurance of health care professionals. So I think that's part of the problem. They don't follow instructions. But I will have a study that will go out and try to identify and quantify a little bit as to what the causes are and what percentage of the problem is associated with that.

I just think a large part of the problem has got to be put to the fact that the physicians that we have that are prescribing medication have very little in the way of pharmacology training, and they have very little in the way of training in the area of geriatric medicine. The two together are a very significant part of the problem; that is, do the physicians really understand, to the degree that they should, what they are prescribing and the effect it has. I think that represents a real problem. As we do more studies along that line, I think we're going to urge upon medical schools that they provide more than a single course in either subject. They need to recognize the fact that, whether we like it or not, the population of the United States is getting older. On that, you're going to have to put more of an accent on training regarding the elderly part of our society.

Mr. Duncan. So you think the real solution, or a big part of the solution, has to be directed at the doctors and the medical schools and the pharmacists and so forth—

Mr. Kusserow. And the patients.

Mr. Duncan. Rather than—

Mr. Kusserow. No, it's not as question of either/or. I think what we're finding here, as we look across—again, it's kind of a broad-brush, kind of global view—is we're finding the problem is not confined to any one part. We need to make progress in all areas. We need to make progress in the basic research and approval process; we need to make improvements in training our physicians in the vital role they have in the links; and the link the pharmacist has has to be improved—there's opportunities for improvements there—and we have to have a better understanding as to how we can communicate better with the elderly in terms of getting them to follow the instructions of their health care practitioners. So I think it's a question of where you can have improvement in all areas. It is not one to the exclusion of the other, but in all areas we need improvement.

Mr. Duncan. I notice in your statement that 17 percent of the population is over 60, 12 percent over 65, and the percentage of prescriptions that go to the elderly and so forth. Do you have any idea as to what percentage of the elderly misuse these drugs?

Mr. Mangano. There's a figure that Dick used a little earlier, that about 45 percent of the elderly use the drugs according to the drug regimen that was outlined by the physician.

Mr. Duncan. I see.

Mr. Kusserow. What I reported in my comments—and maybe I misled you a little bit—I focused on the other side of it. I said that over half do not. Basically, it's half-and-half, half follow instructions and half don't.

Mr. Duncan. I missed that.

Mr. Downey. Would the gentleman yield?

Mr. Duncan. Yes, sir.

Mr. Downey. To what extent is that true in the population as a whole?

Mr. Kusserow. In our report we arranged them by age group. We find that the elderly have more problems with following drug regimens than do other parts.

One thing we're very good about is our children. We make sure our children follow the drug regimen pretty exactly, so you have fewer mismedication problems among them. Now, maybe when we get to be teenagers, we become more lax about doing it. But when we get to be elderly, it seems we have a lot of problems with it. So probably the greatest number that fail to follow instructions is among the elderly.

Mr. Downey. I thank the gentleman.

Mr. Duncan. Just one other quick thing, and this really doesn't apply to your statement today. Did you say that half of all Medicare costs occur in the last 6 months of a patient's life?

Mr. Kusserow. Oh, yes. There is a huge outlay of expenditures in the last 6 months of a beneficiary's life, and that represents the lion's share of payments from the Medicare system.

Mr. Duncan. I didn't realize that. Thank you very much.

Mr. DOWNEY. Actually, the last month of life.

Mr. KUSSEROW. The last month of life is extraordinary. In fact, there is a major debate going on: is that prolonging life or is that prolonging death? That is one, thank goodness, that I don't have to get involved in.

Mr. DOWNEY. We'll leave that to the medical ethicists.

Congresswoman Saiki.

Mrs. SAIKI. My apologies, Mr. Chairman, for arriving so late. Anybody who arrives this late should not be asking any questions, so I will pass for now.

Mr. DOWNEY. You're here, which distinguishes you in large measure from everyone else. Thank you.

Ms. SNOWE. May I ask just one more question?

Mr. DOWNEY. Of course.

Ms. SNOWE. Just a follow up to my question on the two phases which you recommend for the drug utilization reviews.

I understand that GAO is now undertaking a study on the computer capability for the prescription benefit program. Are you aware of that study?

Mr. KUSSEROW. Yes.

Ms. SNOWE. Do you think it's possible that they could recommend—I don't know at this point—the capability for integrating this system?

Mr. KUSSEROW. Not only are they doing it, but I would submit the fact that we're probably doing something far superior than what GAO is attempting to do. That's exactly what we're looking at. Our audit staff is evaluating the plans for implementation, to make sure that we are going to be building a workable system, and that because of an artificial deadline—maybe I shouldn't say this to the Congress, but I consider that an artificial deadline. Given a choice between meeting a deadline or delaying a little bit longer, but making sure you meet the intent of the Congress, I would choose meeting the intent of the Congress. I say this because I have never missed a deadline to the Congress and I don't think missing a deadline to the Congress is a good practice to get into.

The only concern is that you're talking about something that is extremely complicated technically to produce. There is a lot of different ways in which you could begin to develop the kind of network that is being called for. What I would hate to see is the Federal Government outstrip their capability and put in something that would not meet the intent of Congress just to meet the deadline. I think that would be stupid and I would hate to see that.

Ms. SNOWE. Thank you.

Mr. DOWNEY. One last question. You mentioned pharmacological training and geriatric training in medical schools. Have you surveyed them all?

Mr. MANGANO. That information came from prior studies that were done in the field. Much of our report relied on prior studies in areas that we were not able to get into.

Mr. DOWNEY. Our subcommittee would be interested in working with you in developing possibly some sort of faster method of assessing what level of training is given in medical schools at this level, and then possibly issuing a report card on the medical schools, and then maybe looking toward an effort to mandate them to provide a different level of—Do you have any idea of who does a good job now and who doesn't?

Mr. KUSSEROW. We can give you that kind of information, but I would also commend you to discuss that same point with the next witness. This is a pet subject for Dr. Young. We have talked about it on many occasions and he feels very strongly about working in this area. He comes out of that kind of a background. So I think he would be well-suited for that.

Mr. DOWNEY. We will do that and work with his staff as well.

We found, at least in the other subcommittee that I chair, that doing these sort of evaluations and issuing some sort of statement is interesting and even on occasion useful.

Mr. MANGANO. If I might add one footnote to this, one of the studies that we report within our report was a study done by researchers at Temple University which developed a standard test dealing with geriatric pharmacology. They administered that test to a number of physicians in the Philadelphia area and found that either 70 or 80 percent of those physicians failed that test. So the job is not good.

Mr. KUSSEROW. Please do, Mr. Chairman, follow up with us on that, and we will follow up with you in terms of seeing if we can give you a better insight on that aspect of the problem.

Mr. DOWNEY. I want to discuss that with the subcommittee members, too. This may be an area for us to pay a lot more attention to.

Thank you, Mr. Kusserow. You have been terrific.

Mr. KUSSEROW. I thank you.

Mr. DOWNEY. The subcommittee is pleased and honored to welcome its next witness, Dr. Frank Young, who is the Commissioner of the Food and Drug Administration. Dr. Young.

I understand you got up early today to appear on television, so we are delighted that you are with us. This is the beginning of a long day.

STATEMENT OF FRANK E. YOUNG, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ACCOMPANIED BY GERALD FAICH, DIRECTOR, OFFICE OF EPIDEMIOLOGY AND BIOSTATISTICS; DR. ROBERT TEMPLE, DIRECTOR, OFFICE OF DRUG EVALUATION; AND ALEXANDER GRANT, ASSOCIATE COMMISSIONER, OFFICE OF CONSUMER AFFAIRS

Dr. YOUNG. Mr. Chairman, I get up early every day. I left on Monday at 5:45 in the morning to go down and participate in a "bust" on steroids with my colleagues from the FBI, from Miami Vice, the Attorney General's office and the Postal Service in Florida. So I'm used to doing patrol.

Mr. DOWNEY. How was the bust? Was it successful?

Dr. YOUNG. It was the largest single bust that was done in the United States. We apprehended the largest two clandestine laboratories that were providing illegal steroids to the Maryland, Virginia and D.C. area. The two individuals pled guilty, and we hope that they will be serving a good amount of time. We only wish that Congress had more authority for us to put them behind bars for a longer period of time.

Mr. DOWNEY. Amen. We are here on another subject today—I suspect we could talk about anabolic steroids at some length. Could you proceed with your testimony.

Dr. YOUNG. Yes. May I please introduce the individuals that I have with me. On my immediate left is Dr. Faich, who is the individual who is expert in our adverse drug reaction program and supervises that. On my immediate right is Dr. Robert Temple, who is director of one of our drug review offices. Next to him is Mr. Alex Grant, who is Associate Commissioner for Consumer Affairs.

I would like to thank you for having this hearing. It is extremely important that these issues be brought to the American people. I am delighted to have another New Yorker chairing this, and Ms. Snowe, as well as Mr. Duncan and Ms. Saiki here with us.

I would like to submit my testimony for the record, and I would like to make a number of points before this—

Mr. DOWNEY. Without objection.

Dr. YOUNG. If I could please have the visual put up for me so that I can explain some of these issues for you. Please, if you would turn it so the Chairman and the panel can see that.

Dr. YOUNG. I would like to discuss the three major issues that are appropriate for consideration for not only geriatric medicine but medicine in general. I would like to point out that I've had the opportunity before coming into Government service 5 years ago to be Dean of the School of Medicine and Dentistry at the University of Rochester and Vice President for Health Affairs, and one of your later witnesses, Dr. T. Franklin Williams, was the one who has been leading in our community and work on the aging and whom I selected to establish a Center on Aging for our university. It is a field which I have been committed to for a number of years and thus I am delighted to be here.

The points that I would like to make are the following—and Mr. Kusserow emphasized this and you have emphasized it in your statement. But it must be emphasized again that approximately 12 percent of the elderly population consumes 30 percent of the drugs.

The second point is that wherever there is more disease, which does occur in the elderly population—86 percent of the people over 65 years of age have one or more chronic disorders—wherever there is more disease, there is a higher likelihood of adverse reactions. But on the plus side there is absolute evidence—and I have summarized this in Attachment 3 and Attachment 8—that focuses on the increase of quality of life and the length of life through the medicines that are present today.

Third, I would like to point out that we have approximately 26 percent of the adverse drug reactions from the elderly, which constitutes 12 percent of the population, and that as we look at this, as your dialogue back and forth with Mr. Kusserow indicated, the normalization of these to the number of drugs taken indicates that the frequency of adverse drug reactions is not, I repeat, not higher in the elderly population. That's an important issue to look at. We're dealing with a population that has more disease, that takes more drugs, and therefore we would expect to have this. You have to normalize this out.

I would like to read for the record a small portion of a scientific article that I will include for you. This is in the Journal of the

American Geriatric Society, and it's an article in 1988. It points out that it has been consistently shown that the incidence of adverse reactions increases with the number of drugs taken. Mr. Kusserow made that point. In hospital studies—and then it gives the authors—it reported that patients who experience an adverse reaction took on the average twice as many drugs as patients with no reaction.

[See Appendix 2, p. 427 for scientific article entitled, "Prescribing for the Elderly."]

Dr. YOUNG. In one study, the severity of adverse reactions was related to the number of drugs taken. Patients with no reactions took a mean of 7.3 drugs; patients with minor reactions, 11.7 drugs; a patient with severe complications took 17.1. A positive correlation between adverse drug reactions and multiple drug therapy has been noted among outpatients. Secondly, it goes on to say the incidence of adverse reactions increases exponentially rather than linearly with the number of drugs given. That's the answer to the question that you asked so appropriately to Mr. Kusserow.

I would like to point out that as we look at this particular pyramid that I have constructed here, the first, and what you focused on is the proper labeling of safe and effective drugs, we began this journey in 1983, as was described, and there are four seminal issues that need to be focused on. The first is that in 1983 Dr. Temple, who is on my immediate right, recognized that there needed to be more elderly in studies. We have now analyzed this, both in 1983 and 1988, and we have begun to complete this '88 analysis—I will give you part of the analysis in a moment. We found that the inclusion of the elderly is now much more than it was in 1983. People over 60 comprised approximately 30 percent of the individuals studied in many of these drugs.

More significant is the second point, the analysis of the data to determine differences in toxicity. This is something that was first addressed in detail in our 1986 draft, and as you heard from Mr. Kusserow, was finalized in 1988 for format and control of clinical and statistical sections within the new drug application. It requires not only that data be submitted but that it be analyzed. That is a very important inclusion.

[See Appendix 2, p. 293 for "Guidelines for the Format and Content of the Clinical and Statistical Sections of an Application."]

Dr. YOUNG. We found that as the effort is focused on what the new drug application needs to be, that a company making an investment of $120 million will certainly follow these guidelines. It is not a feeling that we're naive about this. If you, sir, were to make a $120 million investment, you might like to see this guideline that is being submitted to the record that shows the format and content of those particular areas. Now, the third area that is very important is to discover as many changes in the pharmacokinetic analysis as possible. Here we look at the blood level of drugs in the patient. The pharmacokinetic studies have increased in the elderly, and we are really determining that there is not necessarily a difference in the elderly with all drugs. We have developed—and Dr. Temple can focus on this more—a screen to look at the pharmacokinetic data, and recently, for example, seven of the eight drugs that we studied in 1988 have pharmacokinetic data on the elderly;

six of the eight are focusing on renal abnormalities; six of the eight are looking at these analyses as a function of age. We will have the whole study completed on all of the new chemical entities approved in 1988 and we will send that for the record as soon as that is done. So there has been major progress in this area as well.

To explore the pharmacokinetic differences is another major goal that we outlined in 1983. Studies are now underway broadly, both in the academic and industrial sector, on looking at renal, hepatic, and other focuses as a function of age. I will make my rough notes into a table for you and submit for the record so that you can see this progress. Now, another issue that is very key is are the drugs labeled appropriately. We have a draft regulation now that is up in General Counsel that will require that a geriatric section for use by included in the labeling. That will be in the Physicians Desk Reference. That is a very important part because that makes that information available to the physicians in the community.

The final point that we're working on is the guidelines for the elderly. There are two things that need to be pointed out, and Mr. Kusserow said it gently, and I'll say it more starkly. If you want a job done badly enough, you're likely to get a bad job. Regrettably, this takes a long period of time to put forward, and it's complicated, I must submit, by the fact that as we have had increased responsibilities going all the way from mercury in the swordfish in the area that Ms. Saiki is concerned with, the chickens in the great State of Maine that Ms. Snowe knows about, with salmonella enteritidis in it, to our great problems in New York City, that we went back and looked and saw what Congress has done to the Food and Drug Administration's capabilities.

You have passed, sir, 23 laws since 1980, provided no resources, for which we have diverted 1,700 people out of 7,000 to new responsibilities. It is just a cruel joke on the American people to feel that you can hold an agency accountable if you ask that jobs be done and put deadlines that are unrealistic and then say why wasn't it done. So I think that's an important consideration as we continue to focus on labeling, because we want to do it right as well, just as Mr. Kusserow pointed out.

I think the next point I would like to focus on for you is the need for an informed patient. I could probably best illustrate this to you if I said you were my patient, you came in to see me and I told you that, regretfully, you had a semino of the left testicle and that the normal prognosis for that is that it might be about 5 years. At this point you might stop listening to me when I said the good news is there are a number of drugs that you could use—sisplatinum, osthonomide, mesna. When the bone pain gets too bad, I could put you on possibly valium and then morphine. By this time you might be thinking about your wife, your children, is my will made out?

The need to inform patients in a systematic fashion, not only when they're older but when they're young, is key. The more desperate the disease, the more critical that is as a requirement. I was proud at our medical center, that we really put a lot of emphasis on communication between patient and doctors. One of the points that I think we need to do is to not only provide systematic education for patients, but to help understand what really are adverse reactions. Mr. Kusserow is correct. As you go to doctors in one part of the country and then another, does each one know what the medicine is. Is the patient asking the questions and is the doctor giving the answers.

NCPIE that Mr. Rogers works with, the National Council for Patient Information and Education, is extremely important in trying to bring that forward. The AARP—who you will hear from in a few minutes—with Mr. Gilmour focusing on the 500 leaflets that we've put out for patient education is a key part. The other part deals with the informed and educated physician. I think that parts needs to be emphasized. I will submit for the record an article on medical education response in the 20th century, a success story, that deals with the degree of response. Now, there are other individuals and I, for one, would say the response is not as good as I would like to see. I would like to see more education, more clinical pharmacology, more education in gerontology. As I said earlier, Dr. Williams and I focused on the interdisciplinary center for aging at our university.

I think the time has come—and we've seen a number of major changes in the system. We have seen in the past 8 years an entry of real geriatric concerns, that we really look for ways in which we can help our older population. I gave you a demographic analysis of the increase in the elderly population. The second point. Society is looking at prescription drugs not just for cures but to enhance quality of life, to maintain independence. Those are real seminal issues. The geriatric care is increasing, and I've been pleased that there are physician certifications now in special competence in geriatrics. This is done by the American Academy of Family Practice and the American College of Physicians. Last year, 4,000 physicians opted for that.

Finally, I think we're looking at a trend in the drug development process, a trend at FDA, to establish indices for morbidity and mortality, to try to look at ways in which we can extend life but extend the quality of life, how to deal with that. To have the most sensitive family, community, and home support is very important. I hope Dr. Williams will describe the access system that we built in Rochester, our attempt to get nursing homes to be teaching places, where we could study clinical pharmacology, our focus on the responsibility of the family to help individuals mature, and when ill, and when terminally ill, die with dignity. These are issues that are very critical.

But it is a pyramidal approach. Optimal drug therapy and conclusion therapy requires not only the properly labeled and safe and effective drugs, but informed patients and informed and educated physicians. That interaction, coupled with really a focus first on health and the well-being of individuals, in my opinion, is the proper way to go. I would be happy to answer any questions here and also act as a resource for you as you begin to go down this very, very important road.

[The prepared statement of Dr. Frank Young follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT

BY

FRANK E. YOUNG, M.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SELECT COMMITTEE ON AGING

SUBCOMMITTEE ON HUMAN SERVICES

UNITED STATES HOUSE OF REPRESENTATIVES

APRIL 19, 1989

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman, I appreciate this opportunity to discuss the issue of drug use in the elderly and the Food and Drug Administration's (FDA) role relative to such use. I understand that you are especially interested in our guidelines on clinical research of drugs intended for the elderly, the development of which was noted in the Inspector General's (IG) draft report, "Medicare Drug Utilization Review." I would first like to discuss the general issue of drug use in the elderly, including drug utilization and adverse drug reactions before I address FDA's efforts to provide clinical guidelines for testing drugs in elderly populations.

Demographics and Drug Therapy

The FDA is fully aware of the implications of the aging of America for drug therapy and drug development. As you know, these issues are the same as those identified in the 1983 joint hearing before the House Select Committee on Aging and the Senate Special Committee on Aging. I would like to provide you with some updated information on demographics and drug therapy.

In the United States, people over 65 years of age represent about 12 percent of the population but utilize 30 percent of health care resources and exactly this proportion of medications. These proportions are predicted to increase sharply during the next century as the post-World War II baby boomers enter their geriatric years around 2015. Attachment 1 graphically demonstrates this demographic trend and Attachment 2 shows the percent distribution of personal health care expenditures and population by age group for 1980 and 2040.

Drug therapy is an essential component of the medical care of our seniors and the drug therapy revolution of the past 30 years has made an important contribution to the increased life expectancy we now enjoy. In addition to reducing mortality and major morbidity, drugs can enhance the quality of life and extend independent life expectancy. (Croog, et al., New England Journal of Medicine, 314:1657-64, 1986).

The use of drugs in older patients poses important problems, many related to selecting appropriate doses in the face of altered drug disposition and/or response, and the greater likelihood of concomitant illness or drug treatment. Attachment 3 lists the major physiologic and pathologic changes that occur with aging and their consequences for drug therapy. The most consistent change is a decline in kidney function by about 30 percent from age 30 to age 70. Despite such changes, on average there is a great deal of variability among older persons. There are fit, active persons in their 80's who exhibit none of the frailties and multiple disorders that may affect some of their juniors. Thus, individualization of therapy is essential, and it is critical to have the best possible information available on how to do this.

Drug Utilization

Both the proportion of the total population and the proportion of total drug usage accounted for by the elderly have been steadily rising. The rate of drug use in people over 65 years old is four times that found in the younger population. Studies have shown that the average elderly Medicaid beneficiary is exposed to 10 different drug entities per year and the average HMO member who is over 65 will receive 13 outpatient prescriptions in a year (over twice that of younger members). (Baum, et al., Drug Information Association Workshop on Geriatric Drug Use, Washington, D.C. 1984) (Sokol et al: American Journal Hospital Pharmacy 45:622-623, 1988).

The increased use of drugs by older persons reflects the increased prevalence of disease in this population. Eighty-six percent of persons aged 65 and older have one or more chronic disorders (Klein, et al. JAGS 29:525, 1981). Furthermore, many of these disorders require medication. For example, arthritis is reported by nearly half, hypertension by more than a third, and heart conditions by more than a quarter of those over 65 years of age. Attachment 4 lists the top 15 diagnoses for older persons, and Attachment 5 shows the leading causes of death in this segment of our population. It is clear that cardiovascular diseases are by far the largest health burden to senior citizens.

The types of drugs used most commonly by the elderly are cardiovascular agents and diuretics (36 percent), antiarthritics and analgesics (11 percent), anti-infectives (9 percent), antidiabetics (5 percent) and psychotherapeutics (5 percent). This is slightly different from the categories used most frequently in patients younger than 65 years old which are anti-infectives (20 percent), antiarthritics and analgesics (13 percent), cardiovascular agents and diuretics (12 percent), cough/cold products (7 percent) and psychotherapeutic agents (7 percent). (Drug Utilization in the U.S.-1986:Eighth Annual Review: FDA, 1987). These distributions, of course, reflect the types of diseases usually found in each age group.

Attachment 6 is a listing of the top 25 drugs used in the elderly. Because the list is based on those drugs that office-based physicians specifically prescribe, both brand and generic names appear (e.g. Lanoxin and digoxin). Sixteen of these 25 drugs are either cardiovascular agents or diuretics. Attachment 7 is a listing of the top 20 chemical entities most frequently given to the elderly in hospitals. This list combines branded and generic products together and lists them under their chemical name. Most of these drugs have been available for well over a decade, and it should be possible to use most of them properly in older patients based on current information.

Adverse Drug Reactions (ADR'S):

There is no doubt that adverse drug reactions occur with some frequency in the elderly and the consequences of these reactions are important. Many of the drugs which appear on adverse reaction lists are the same as those which have been shown in large scale, multinational studies to reduce morbidity and mortality (Attachment 8). Among these are antihypertensive agents, beta blockers, drugs for heart failure, aspirin and thrombolytic agents and anti-infectious agents. Most of these reactions are due directly to the known pharmacologic risks of the drug involved. For example, when treating hypertension with agents that lower blood pressure, some degree of abnormally low blood pressure, or hypotension, may occur in some individuals. Similarly, when using insulin to lower blood sugar, hypoglycemia may occur.

Another important aspect of adverse drugs reactions in the elderly is that, with some notable exceptions, rates of reactions appear to be related to the number of drugs taken. That is, there is little scientific evidence that the elderly have, as a general matter, more reactions than other individuals when the number of medications used is taken into account. The data in FDA's reaction reporting system substantiate this conclusion. About 26 percent of reactions reported to us involve the elderly even though they constitute only 12 percent of the population. From these data it might be thought that the elderly have a rate of reported reactions twice that of younger groups. This would be naive, however, as the elderly take about four times the amount of drugs as younger populations. Thus, there is no evidence in our reporting system of an overall increase in their rate of reported reactions per drug taken. This leaves open the possibility, of course, of increased risks from particular drugs.

The Inspector General's draft report tentatively arrived at a different conclusion. That is, the elderly experience adverse drug reactions disproportionately greater than the remaining population. The worldwide literature on this subject, recently reviewed by Nolan and O'Malley (JAGS 36:142-149, 1988), does not seem to support this conclusion. We have provided comments to the IG expressing our concern about some of the evidence presented to support this finding, and we look forward to seeing this issue resolved in the development of the final report.

Whether or not there is an overall increased rate of ADR's per drug, it is clear that adverse drug reactions in the elderly may differ in important ways from those in younger persons. When an elderly individual sustains a reaction, it is likely to be more severe than it would be if it occurred in a younger individual. It is known, for example, that the elderly are particularly susceptible to ADR's related to sedatives and psychotropics. This susceptibility can lead to over-sedation, which may result in falls. In older persons a hip fracture is more likely because of their greater likelihood of osteoporosis. (Ray, et al., New England Journal of Medicine 1987; 36:363-9). In addition, while anti-inflammatory drugs seem to cause gastrointestinal ulcers and bleeding at about the same rate in younger and older people, these events are more likely to be fatal when they occur in older persons.

Our own ADR reporting data show that 32 percent of reactions in the elderly reported to the FDA are associated with hospitalization or death, while for younger individuals this figure is only 22 percent. Of course, the occurrence of an ADR may not represent poor prescribing but simply an inevitable consequence of drug use. For example, a patient with severe arthritis needs treatment to relieve suffering and to increase mobility. Drugs that might be prescribed are likely to precipitate gastrointestinal bleeding. In this instance, the fact that such a patient may develop gastrointestinal bleeding and be hospitalized may be an unavoidable consequence of attempting to improve the patient's quality of life.

FDA's Initiatives

Although much is currently known about drug use in the elderly, we will continue our own efforts and work with the National Institute on Aging, the Health Care Financing Administration (HCFA), and other agencies to improve the quality and accessibility of information related to drug use and adverse effects of drugs being used by elderly populations. Included in this effort are the following specific FDA activities:

1. Preparation of a guideline on the study of drugs in the elderly.

2. Development of regulations requiring that information related to use of drugs in the elderly be placed in a special section in drug labeling, which is intended primarily for use by the physician.

3. Special attention to tracking the early postmarketing experience of new drugs likely to be used at a high rate in elderly populations.

4. Postmarketing research activities focused on elderly populations, taking advantage of large automated data bases to study drug usage and risk. These databases include Medicaid and Group Health Cooperative at Puget Sound. We will also seek to use data from the Veterans Administration and Medicare.

5. Association with HCFA in that Agency's implementation of the Medicare Catastrophic Coverage Act of 1988 over the next several years in order to see how information collected in conjunction with this program can be used to improve quality and quantity of information about drug use in the elderly.

Clinical Guidelines

Your letter of invitation asked that we particularly address the current status of FDA's guidelines to manufacturers to ensure the adequate testing of drugs in elderly populations, as cited in the Inspector General's draft report. In 1983, in response to a growing perception within and outside FDA that drugs used by the elderly were not being studied adequately, Dr. Robert Temple, Director, Office of Drug Evaluation, with the advice and support of FDA and National Institute on Aging staff, prepared a discussion paper on testing of drugs in the elderly, a "prospectus" for an eventual guideline. I would first like to describe our efforts to date in this area. Generally, these have been considerable and have already effected significant portions of the guideline we proposed in 1983, although we have a few further steps to complete.

I will use the principles outlined in our discussion paper of 1983 as the context for relating the progress made to date. A full discussion of that paper would be too time-consuming for presentation here, but its main features and premises are simply stated:

Premise 1: Elderly patients should be included in studies of any new drug with probable use in older patients. They could be included along with other patients in studies or entered into specific studies in the geriatric patient.

Although the IG draft report stated that drugs are studied in young healthy people and given to elderly patients with diseases, a survey in 1983 of 12 pending or recently approved new drug applications (NDA's) showed that, in fact, older patients were regularly included in clinical studies of new drugs. Thus, even before any FDA efforts to stimulate their inclusion, older patients were included in studies. To cite some specific figures:

- For 3 non-steroidal anti-inflammatory drugs, benoxaprofen (Oraflex), ketoprofen (Orudis), and zomepirac (Zomax), 22-36 percent of patients were over 60 and 8-11 percent were over 70. In these cases 519 to 1237 patients over 60 were included.

- For 2 antibiotics, cefoperazone (cofobid) and netilmycin (Netromycin), 34 and 30 percent of patients were over 60 and 17 and 19 percent were over 70.

- For an antianginal drug, verapamil (Isoptin), 35 percent of patients were over 60, 7 percent over 70.

- For triazolam (Halcion), 12 percent of patients were 60 or over, but this represented 517 patients, including 13 trials carried out specifically in elderly patients.

We have recently carried out a second review, this time covering all drugs approved in 1988. I hope to be able to provide the results of this review shortly.

While we still intend shortly to provide a guideline explicity stating the need for studies of new drugs in older patients, exclusion of elderly subjects from trials is not a major problem, at least with respect to patients in their 60's and 70's.

> Premise 2: There should be an analysis of the data in NDA's to see whether effectiveness or adverse effects are influenced by age or by other factors that might be more common in the elderly, such as concomitant drug use or concomitant illness.

Although we found that older patients were included in studies, we also found that little use was being made of the data to see if age was relevant; e.g., whether there were more episodes of particular adverse effects in older patients. This was part of a more general problem. Data bases were not being analyzed for possibly important influences of demographic features (age, sex, race) or concomitant conditions.

We did not wait for the preparation of the guideline on study of drugs in the elderly to deal with this matter. Instead, the need to evaluate data in this fashion was stressed in an extremely important regulation, the Guideline for the Clinical and Statistical Sections of an Application, proposed in 1986 and made final in July 1988. Two sections, describing the format and content of the integrated summaries of effectiveness and of safety data, repeatedly emphasize the need for analysis of the influence of such variables as age on the results of trials.

We are now seeing such analyses regularly in NDA's, although not in all, as some applications were prepared before the guideline. The new data are reflected in labeling for many recent drugs, such as nicardipine (Cardene), a drug for angina and hypertension; nizatidine (Axid), an anti-ulcer drug; fluoxetine (Prozac), an antidepressant; and lisinopril (Prinivil), an antihypertensive, each of which was subjected to the kind of analysis called for in the Guideline.

> Premise 3: It is critical to discover all (or as much as possible) of the ways that the pharmacokinetics of a drug (i.e., how the drug is metabolized and excreted by the body) can be different from one individual to the next, because most of the recognized differences between individuals in their responses to drugs result from these pharmacokinetic differences. However, pharmacokinetic information is not uniquely relevant to the elderly, and age per se is not the most important factor that affects how older people handle drugs. Rather the conditions more frequently found in older people, such as decreased kidney or liver function, heart failure, decreased lean body mass, and use of other drugs, are the major problem. These conditions can occur in people of any age but are more likely in the elderly. What is critical is to understand the influence of such conditions. When we do, not only the elderly will benefit, but the information will be of value in patients of all ages.

We are in the middle of an explosion of pharmacokinetic information that will lead ultimately to a greatly enhanced ability to select appropriate doses of drugs for patients, i.e., to individualize treatment. We know much more about how altered kidney or liver function affects particular drugs, and we recognize that there are many individual genetic differences that can have major effects as well. Also, the concomitant drugs a person takes can have profound effects on other drugs. Some years ago, for example, it was discovered that quinidine and verapamil, drugs for cardiac arrhythmias and angina, both common conditions in the elderly, increased the blood concentrations of digoxin, a major drug for heart failure, which is commonly used in the elderly. More recently, and perhaps more far-reaching, evidence indicates that quinidine markedly alters the metabolism of all drugs metabolized by an important liver enzyme by profoundly inhibiting the action of that enzyme. This will affect the metabolism of a number of antiarrhythmics, beta-blockers and, although not yet fully explored, many other drugs. Obviously, such discoveries are relevant to everyone using the interacting drugs, but this concomitant use is more likely to occur in older patients.

In considering how the many possible, but not yet recognized, factors that could alter pharmacokinetics might best be evaluated for a new drug, there are two possible approaches. One is to use available information on how the drug is excreted, metabolized, and used in therapy to decide what specific studies are needed. For example, for any drug excreted intact by the kidneys, there should be a study of how blood levels are altered in people with varying degrees of renal failure. This is in fact standard practice today. For drugs used to treat heart failure or angina, there should be a study of effects of concomitant digoxin use, because digoxin would commonly be used together with such drugs and has a narrow therapeutic index, so that changes in its pharmacokinetics would be important.

We do not think, however, that we usually know enough to reason out all of the possible problems so that all reasonable studies can be carried out. We therefore proposed a "pharmacokinetic screen." This involves taking one, or a few, blood levels of a new drug in essentially every patient. The blood levels would then be examined to see if various conditions had an effect on them. For example, are blood levels regularly higher (or lower) in older patients, women, or blacks? Are they higher in people who are too fat or too thin, who have heart failure, who are on other drugs, etcetera? Are there particular individuals who are marked outliers without obvious explanation, perhaps suggesting genetic differences in metabolism or excretion?

We thought the screen represented a simple, relatively inexpensive means of finding important unanticipated inter-individual differences. The idea, being novel, was somewhat controversial, but engendered extensive constructive comment from industry and academia. Recently, a committee of the American Society for Clinical Pharmacology and Therapeutics (ASCPT), after reviewing results of a joint FDA-ASCPT workshop in 1984 and subsequent pilot tests of pharmacokinetic screens, endorsed the proposal as a reasonable (but not necessarily the only) component of the pharmacokinetic evaluation of new drugs.

The guideline for study of drugs in the elderly will address the issue of how best to discover the factors that influence drug excretion and metabolism, a matter of special relevance to the elderly. It will reinforce a process that is already underway, a process stimulated by FDA's requests in its review of new drugs for information on effects of concomitant disease or drugs and on how drugs are excreted and metabolized. Labeling of many new agents already reflects such information, i.e., what dosage adjustments are needed in patients with liver or kidney dysfunction and effects of other drugs.

Premise 4: Apart from differences in pharmacokinetics that can lead to different blood levels despite the same dose, there can be differences in how a drug affects people, i.e., differences in response to the same dose. These are called pharmacodynamic differences. Some of these are recognized as age-related. For example, older people appear to respond less to beta-blockers because they have fewer beta-adrenergic receptors to be influenced. Older people also appear to respond more to such sedating drugs as benzodiazepines (drugs like Valium), so that lower doses should generally be used, a fact recognized in labeling of many of these agents. There are, in addition, known race-related differences and differences related to the pathophysiology of a patient's disease. Blacks with hypertension, for example, on the average respond less well to beta-blockers and ACE inhibitors than do whites, perhaps because they tend to have low-renin hypertension, which is known to respond less well to these drugs.

For the most part, we believe it should not be necessary to carry out specific pharmacodynamic studies in the elderly. Rather, if the elderly are included in clinical trials, important differences in response should be discernible in the analyses described above. In fact, separate trials of the elderly have the disadvantage of not permitting direct comparisons with responses in younger patients. Suggestions of differences that emerge in clinical trials might, of course, need to be followed up with more targeted trials in older patients. An exception to this general plan would be made where special problems can be anticipated. For example, dose-response relationships in older patients for drugs that are highly sedating should be studied.

As I indicated, the 1983 discussion paper has been discussed widely and its most important suggestions, inclusion of older patients in studies and analysis of age-related effects in trials, have been effected to a large extent. Numerous workshops and discussions that we have sponsored or participated in have now led us to the point where we believe the pharmacokinetic aspects of the discussion paper can be incorporated into a formal guideline. We will proceed rapidly to do this; in fact, a draft guideline has just begun circulating internally.

The explosive growth of information related to use of drugs in the elderly, and the prospect of a further increase, led us to conclude that we should change the labeling regulations to require the section on geriatric use in drug labeling, similar to the one for pediatric use that has long existed. That section will describe available information or indicate that data on the elderly are not available. We intend also to ask that the pharmacokinetic data in current labeling be updated.

We are proud of our efforts to date. While we wish the guidelines were complete in all respects, major parts have been implemented and the rest will be completed soon. The proposal for the pharmacokinetic screen represents a major innovation that we think will lead eventually to a great increase in information allowing individualization of therapy to make it safer and more effective. There has been very substantial agreement in government, academia, and industry on the need for better data on use of drugs in the elderly.

Finally, let me note that there are remaining problems to which we do not yet have good answers. As I have indicated, there is a reasonable representation of patients in their 60's and 70's in clinical trials; however, very old patients, i.e., patients in their 80's, and the so-called "frail elderly," very ill patients with multi-system disease, are not usually included in large numbers, although there are exceptions to this. It may prove very difficult to include such patients routinely. They may present problems in complying with drug regimens. Sponsors may fear to expose these patients to experimental drugs. In outpatient studies, these patients may have difficulty getting to the clinic. One might also ask whether it is appropriate to study a relatively unfamiliar agent in notably fragile people unless the new drug represents a significant gain. Our experience with antiarrhythmics, for example, is that sicker patients, i.e., those with heart failure, coronary artery disease, and more severe arrhthymias, are much more susceptible to the serious adverse effects of the drug. In that case, of course, they may need the drug anyway, but for drugs of lesser importance, perhaps they should be spared unnecessary exposure.

While we will continue to press the idea that patients in trials should be more representative of the full range of patients expected to get the drug, I would not want to imply that this last problem is readily solved. But by learning more about what influences drug response in people of all ages, we will have a better data base for extrapolation into those extremes of age and complexity.

Comments on IG Draft Report

The IG's draft report is in many respects an accurate representation of the difficulties involved in treating elderly patients and of the need for better education and more geriatric information. We share the view that every drug with potential use in older patients should be studied in such patients and labeled properly for use in them, and we have taken many steps toward this goal. The guideline under development will shortly be completed. As I mentioned earlier, we are in the final stages of development of a proposed regulation that would require a "Geriatric Use" section in all labeling, both for newly marketed products and, after a period of time, for previously marketed products.

This regulation is needed to be sure that all labeling is optimal. An internal FDA survey, however, indicates that 212 of the 425 individual drugs used most often by the elderly (50 percent) contain geriatric information and that 10 of the top 24 (42 percent) used in the elderly already contain such information. These percentages are significantly higher than those cited in the draft IG report. The differences may be due to the fact that the FDA survey is more specifically targeted toward the drugs the elderly are actually taking, while the IG report includes the popular top 200 drugs for all age groups, such as oral contraceptives or pediatric antibiotics. This information is readily available from our Department's own database: "Drug Utilization in the U.S. - 1986, 8th annual review." Additionally, while the IG draft report appears to have searched for geriatric information only in the "Adverse Reactions" or "Dosage and Administration" sections of drug labeling, our survey found a great deal of geriatric information in other commonly used sections such as "Precautions," "Warnings," "Clinical Pharmacology," and "Contraindictions." We look forward to seeing these inconsistencies resolved in the final report.

Patient Education

Optimal drug therapy requires safe and effective drugs, informed health care providers, and informed patients. Achieving these three essential components presents multifaceted challenges throughout the drug development and delivery system. I have previously discussed the progress that FDA has made in meeting the scientific goals related to safe and effective medications for the elderly. I would like to briefly discuss the two other essential components of this therapeutic triad --- the informed patient and the informed health care provider -- as they relate to the elderly.

Patient education is the most effective approach for assisting consumers in their efforts to use medicines safely and effectively. In the best of all worlds, we would begin to develop good habits in the proper use of medications -- both over-the-counter and prescription medicines -- in our younger years and increase these over the course of our lives. While this is a goal that we should continue to strive for, the reality for the elderly today is that patient education has become a necessity at a time when medication use is most complex.

As indicated in the Inspector General's draft report, educating elderly patients regarding their medications requires cooperative ventures between the public and private sectors. FDA has worked jointly with many organizations in both sectors representing the interests of the elderly to gain their views on the patient education needs of the elderly and to design programs responsive to these needs.

As an example of these cooperative programs, FDA has a long-standing relationship with the National Council for Patient Information and Education (NCPIE). NCPIE is a consortium of over 200 independent organizations with a stake in improving patients' knowledge about their medications. Over the past several years, FDA has worked with NCPIE to help improve the quality of patient education by improving the quality of doctor instructions and encouraging patients to ask doctors, nurses, and pharmacists about medication use. With the increased prescription drug use among the elderly, NCPIE together with FDA and other organizations has focused much of its efforts in targeting prescription drug information to the elderly. The 1987 "Talk About Prescriptions" month emphasized the problem of improper drug use among the elderly. In association with this effort, NCPIE conducted a public education campaign to improve communications between health professionals and elderly patients.

FDA also has a long standing relationship with the American Association of Retired Persons (AARP), and we have worked jointly with their pharmacy service to develop patient education materials for the elderly. One of the services that has come from this partnership is the Medication Information Leaflets for Seniors (MILS) program. MILS, which are informational leaflets for specific drugs, inform the patient what the drug is, what it is used for, how to take it, what side effects to be aware of, and what questions to ask the prescriber. MILS are provided to AARP members through a mail-order prescription program or by request. Since the inception of the MILS program in 1981, the FDA and the AARP pharmacy service have cooperatively authored 93 leaflets covering 500 drugs which represent 90 percent of the drugs that the AARP dispenses.

In addition to producing MILS, we plan to initiate a market research program with the AARP pharmacy service to understand better how elderly patients learn about their medication. This will enable additional programs to be developed that are best suited to the needs and desires of the elderly.

It is beneficial to raise the awareness of elderly consumers about using medicines safely and to promote programs to encourage the elderly to become informed patients. However, patient education, particularly for the elderly, should be institutionalized within a system where there is accurate and individualized communication about medication use, reinforcement and monitoring from a variety of sources (including allied health professionals, families, friends, and community organizations), and regular followup. Within our health care structure, this basic system is the physician-patient relationship.

The third part of this optimal therapy requires that physicians: 1) are aware of the aging process and the individual differences of their patients; 2) know what problems to look for in the elderly patient that would indicate evidence of a disease condition; and 3) be informed about therapeutics involved in that patient's care. The American College of Physicians recognizes the need for physician education and has issued a plea for improving medical education in therapeutics (Ann. Int. Med. 108:145-147, 1988). Similarly, the medical community is also concerned that medical education in geriatrics, while improving, is still inadequate to meet current or future needs (J. Am. Ger. Soc. 35:1107-1115, 1987). We also recognize the need for educating physicians, and we do so in the context of our responsibility for the information provided in the drug labeling. We 1) periodically publish a Drug Bulletin containing information of importance to physicians and other health care professionals, 2) provide a monthly column on drugs for publication in the Journal of the American Medical Association,

3) have supported projects in several states on how health professionals should report adverse drug reactions so that the Agency can use the data to help insure safe use of marketed products, and 4) publish a list of unapproved drugs that are available under Treatment INDs, ie., investigational new drugs available for treatment of patients.

Clearly, physicians and other health care providers must be proficient in geriatrics and in rational drug therapy to suitably utilize the guidance provided by the FDA in labeling and other communications. The Agency will continue to work with NCPIE to encourage health care professionals to discuss medication use with their patients, to become familiar with their patients current medication use (both prescription and over-the-counter) and obtain information essential to safe and effective medication use. Other components of the government, however, have a more direct involvement in physician education and training.

Conclusion

FDA has a strong interest in ensuring that the interests of our elderly patients are taken into account in the drug development process. This includes not just appropriate participation in clinical trials, but appropriate labeling as well. We are also strong advocates of consumer and physician education and awareness. Without an informed citizenry, our efforts on their behalf can never be fully successful. In this regard, we have carefully recorded and analyzed data on adverse drug reactions in the elderly, so that important information can be identified and disseminated to the medical community. Our approach to the clinical guideline for study of drugs in the elderly has been made widely known to the drug industry, which, for the most part, already has implemented its objectives. Nevertheless, we are in the process of completing this guideline.

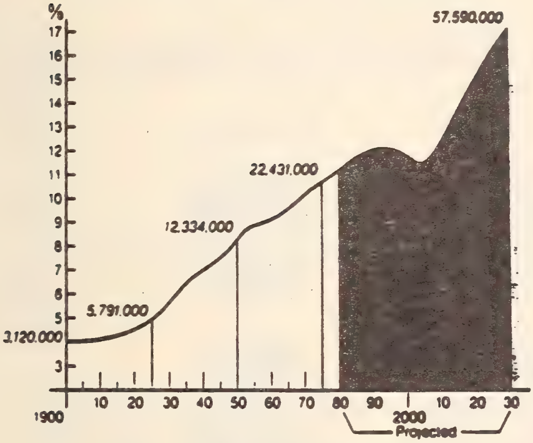
Labeling of recent drugs often reflects specific information related to use of drugs in older patients. Surveys by FDA have shown that approximately 50 percent of the products used most often by the elderly already include labeling with specific information pertaining to their use in the elderly, and the Agency is preparing to publish a regulation that will formally require such labeling.

Though this is not a simple issue, much has been accomplished to provide greater assistance to the health care provider on the use of drugs in the elderly. We will continue to work with this Committee and all of the health agencies involved and with the pharmaceutical industry to build upon these accomplishments.

I will be pleased to respond to your questions.

Attachment 1

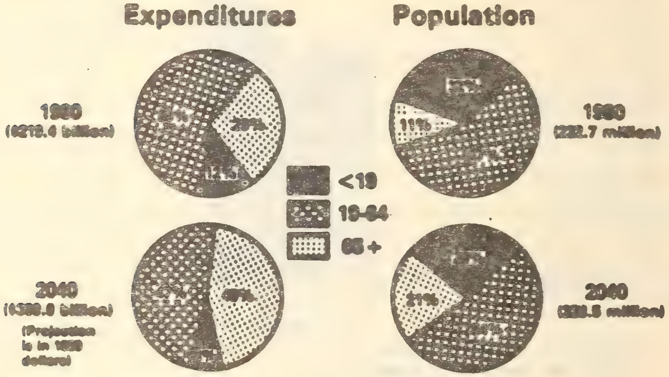
Percent of U.S. population aged 65 and older, 1900–2030.



Vogt, T.M., 1986. From Butler, R.N.,
NIH Publication No. 80-969, 1980.

ATTACHMENT

Percent distribution of personal health care expenditures and population by age group and year



SOURCE: Projected from Health Care Financing Administration estimate for 1978

ATTACHMENT

Table 1

CHARACTERISTICS OF THE ELDERLY RELATIVE TO DRUG DISPOSITION AND RESPONSES[a]

Reduced renal function: accumulation of renally cleared drugs
Reduced serum albumin levels: increased free drug
Relative increase in body fat: increased distribution volume of fat-soluble drugs
Reduction in body size: decreased distribution volume of water-soluble drugs
Reduction in liver metabolizing capacity: accumulation of metabolized drugs
Increased sensitivity to CNS drugs: adverse effects
Decreased cardiac reserve: potential for heart failure
Decreased baroreceptor sensitivity: tendency to orthostatic hypotension
Decreased vital capacity and maximum breathing capacity: increased risk from beta blockade and CNS depression
Oversecretion of antidiuretic hormone: potential for water intoxication
Concurrent illnesses: disease interactions
Multiple drugs: drug interactions
Large interindividual variation: wide dose range

From Abrams, W.B., Rodda, B.E.: Chapt. 18, Clinical Trial Design - Industry Perspective. In: "Drug Studies in the Elderly," Neal R. Cutler and Prem K. Narange (eds.), New York City, Plenum Publishing Corporation, 1986, p. 356. (with permission)

ATTACHMENT 4

TOP 15 DIAGNOSES FOR OLDER PERSONS (65+)

1985-1986

	65+	65-84	85+
1.	Hypertension	Hypertension	Congestive Heart Failure
2.	Surgical aftercare*	Surgical aftercare*	Hypertension
3.	Congestive heart failure	Diabetes	Surgical aftercare*
4.	Diabetes	Angina	Angina
5.	Angina	Congestive heart failure	Arteriosclerotic heart disease
6.	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	Hypertension heart disease - other
7.	Hypertension heart disease - other	Hypertension heart disease - other	Arrhythmias
8.	Arrhythmias	Osteoarthritis	Diabetes
9.	Osteoarthritis	Arrhythmias	Osteoarthritis
10.	Arteriosclerotic heart disease	Glaucoma	Glaucoma
11.	Glaucoma	Arteriosclerotic heart disease	Urinary tract infection
12.	Bronchitis	Bronchitis	Hypertension arterio-sclerotic - other
13.	Urinary tract infection	Arthritis	Cerebral hemorrhage
14.	Hypertension arterio-sclerotic - other	Urinary tract infection	Pneumonia
15.	Arthritis	Hypertension arterio-sclerotic - other	Chronic obstructive pulmonary disease

*Various conditions associated with post-surgical care

Source: IMS NDTI, 6/85 - 5/86

ATTACHMENT 5

LEADING CAUSES OF DEATH IN OLDER PERSONS (65+)

1983

Cause	Rates per 100,000			
	65+	65-74	75-84	85+
All causes	5,110	2,870	6,440	15,170
Diseases of the heart (primarily myocardial infarction)	2,230	1,140	2,820	7,340
Malignant neoplasms (primarily of digestive organs, peritoneum, respiratory, intrathoracic, and genital organs)	1,030	830	1,260	1,580
Cerebrovascular diseases	490	180	650	1,910
Chronic obstructive pulmonary diseases	190	140	260	310
Pneumonia and influenza (primarily pneumonia)	170	50	210	860
Diabetes	100	60	130	210
Atherosclerosis	90	20	100	530
Accidents and adverse effects	90	50	110	260
Nephritis, nephrotic syndrome, and nephrosis (primarily renal failure or impaired renal function)	60	30	80	190
Septicemia	40	20	50	130

Source: National Center for Health Statistics, Vol. 34, No. 6

Note: Rates rounded to nearest 10.

ATTACHMENT 6

Table 1: THE TOP 25 SPECIFIC DRUGS USED BY THE ELDERLY
(In Rank Order)

Lasix
Lanoxin
Dyazide
Digoxin
Hydrochlorothiazide
Inderal
Aspirin
Persantine
Theo-dur
Nitroglycerin
Insulin NPH
Coumadin
Prednisone
Aldomet
Procardia
Isordil
Motrin
Tylenol with Codeine
Tagamet
Cardizem
Capoten
Tenormin
Lopressor
Tomoptic
Zantac

Source: National Disease and Therapeutic Index, 1986.

ATTACHMENT 7

Table 2: THE TOP 20 CHEMICAL ENTITIES USED BY THE ELDERLY IN THE HOSPITAL
(In Rank Order)

Furosemide
Acetaminophen
Potassium Chloride
Heparin
Nitroglycerin
Aluminum/Magnesium Hydroxide (s)
Digoxin
Ranitidine
Meperidine
Cefazolin
Docusate
Triazolam
Lidocaine
Bisacodyl
Diazepam
Aspirin
Morphine
Hydroxyzine
Dipyridamole
Nifedipine

Source: International Health Services (IHS) Hospital Data Base, 1987.

Attachment 8

LARGE SCALE STUDIES SHOWING REDUCTION IN MORBIDITY AND MORTALITY

1) Antihypertensive agents (Amery, A., et al., The Lancet, 5/15/85, 1349-1354; MRC Trial of Treatment of Mild Hypertension, Br. Med. J. 291(6488):97-104, 1985; Hypertension Detection and Follow-up Program Cooperative Group, JAMA 259(14):2113-2122, 1988).

2) Beta-blockers (Yusuf, S., et al., Progr. Cardiovasc. Dis. 27:335-371, 1985).

3) Drugs for heart failure (Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), New Eng. J. Med. 316:1429-1435, 1987; Mulrow, C.D., et al., JAMA 259:3422-3426, 1988).

4) Aspirin (Lewis, H.D., Jr., New Eng. J. Med. 309:369-403, 1983).

5) Thrombolytic agents (Stampfer, M.J., et al., New Eng. J. Med. 307:1180-1182, 1982).

6) Anti-infectious agents (Barker, W.H. and Mullooly, J.P., JAMA 244:2547-2549, 1980; Shapiro, E.D. and Clemens, J.D., Ann. Intern Med. 101:325-330, 1984).

Mr. Downey. Thank you, Dr. Young, for your testimony. It has been very helpful.

I was about to start off with a chronology of questions about clinical guidelines for testing the elderly, reciting some of the various milestones that we passed. But I think you've given us a pretty good idea that this is a vastly complicated area.

Dr. Young. Yes, it is.

Mr. Downey. Not only that, but it is one that we have asked of your agency more and more and have provided you less and less. The only place I know that works is in light beer. It doesn't usually work with—

Dr. Young. It has been a problem. You saw us working with a major fruit issue in our part of the country, where it comes into the Philadelphia port. We diverted over 400 people out of our force of 800 to work on that problem.

Mr. Downey. I don't want to be pejorative here, but waiting for the guidelines is a bit like saying "your check is in the mail". It will be here in just a few more months. Can you give us some idea of when they're going to be ready, what we're looking at in terms of a time horizon?

Dr. Young. Surely. Let me point out one particular issue that may not be fully comprehended. When FDA sneezes, the world gets pneumonia. By that I mean that, once we start down a line to guidelines, we have multiple conferences, multiple interactions with industry, and that moves very rapidly into force.

In the case of guidelines, we felt that the first thing we needed to do really was to put out the clinical guideline and requirements. That's the document which says, if you are going to submit a new drug application from Downey ABC Drug Development Company, you have to put this in it. Once you get that message, your responsibility is very clear and, with your $120 million investment, you are not going to avoid that. That has already been done and that was the book that I held up.

Now, what we're focusing on in the guidelines is really the second step, how to do it, and give that guidance. Now, we have given that informally. We have spent a lot of discussion with the companies. The particular guideline Dr. Temple has been working on vigorously, and that, he assures me, is leaving his office and coming up to my office. In that sort of a tracking system, we're probably looking, Bob, at about 6 months at the minimum, to a year on the outside, or less. What's your—

Dr. Temple. A draft actually just circulated to a number of people as of yesterday. I think we'll have it out in a few months.

Dr. Young. The most important thing is the same way that Mr. Kusserow circulated his draft. If we are to put something out which is not realistic for both the clinical investigators and for the industry, we will be doing harm rather than good. So a lot of the part is the development of consensus to deal with this process. That has been an important issue. We feel we've made a lot of progress by doing it in a careful way.

Mr. Downey. In your testimony you state, "There is little scientific evidence that the elderly have, as a general matter—" and I think this was the initial point you made "—more reactions than other individuals when the number of medications used is taken into account." And you add that the Inspector General's draft report tentatively arrived at a different conclusion.

Could you give us some idea of why the differences in those conclusions?

Dr. YOUNG. Surely. We have discussed that in detail, as you could imagine. The Inspector General has focused on a lot of our comments. We came at it, as he said, from an apple and a pear approach. As we have looked at this together, I can tell you that his final report, which will be issued in a few days, will reflect the complete resolution of our differences. It depends on how you normalize. If you normalize for a number of drugs, you will come up with the exact conclusion. What I will do is introduce for the record approximately four other references, so that it will be within the record, that will clearly show this particular point.

For example, in the epidemiology of adverse reactions—and I quote from the article of Nolan—"The evidence for an increase in the incidence of adverse drug reactions with the increase in patient age is by no means definitive. While some investigators have found a positive correlation between patient age and incidence of adverse affects (references 10 to 17) many more have failed to demonstrate this relationship (references 18 to 25)."

[See Appendix 2, p. 427]

Dr. YOUNG. Now, as you look at this very complicated issue, you have to go study by study and analyze these. The bulk of the scientific consensus at this snapshot moment is that there really does not seem to be this correlation. It goes on to say that "discrepancies are due, in part, to differences in population under studies and methods of detecting unwanted effects, and the definition of adverse reactions."

Mr. DOWNEY. Okay. Let me see if I understand it. If you can explain it to me, you can explain it to anybody else.

By normalization, you mean that if in a study we take, as an example, people who take a lot of drugs, regardless of age, that the likelihood of misapplication and misuse is greater—

Dr. YOUNG. That's correct.

Mr. DOWNEY. {Continuing] and that since the elderly take more drugs or are more susceptible and necessary to take more drugs, this is the difference that we see statistically?

Dr. YOUNG. That's correct, and it also depends on the drug itself. You're likely to have much more adverse reactions in Digoxin, for example. That constitutes about 20 percent of the adverse reactions. Then there are subpopulations that have kidney disease. In that subpopulation with kidney disease you're likely to have more adverse reactions with drugs that influence hepato-renal access. So there are a lot of variables. But the bulk of the consensus at this time is that nondifference is a function of age. Just no difference at all.

Mr. DOWNEY. Dr. Temple apparently in an earlier report indicated that there was some question about using phermaco-kinetic screens, and in your testimony you said there was some controversy in this. Can you elaborate on that?

Dr. YOUNG. Please let Dr. Temple do that, if you will.

Dr. TEMPLE. Let me briefly define what that is and why we thought it was a good idea.

Most people who consider the geriatric drug problem believe that the major problem is that, either because of age or because of conditions that are associated with age, like declining renal function or heart function or whatever, the way older people handle certain drugs is different from the way young people handle them. If they handle them by accumulating more of them, they're more susceptible to getting into difficulty.

The failing functions of the patient, the fact they're on other drugs, the fact they have other diseases, all can contribute to this. What the physician needs to know is what these influences are so he can make appropriate dosage adjustments. That's the information base the physician needs.

There are two possible things you can do. You can try to be smart and figure it out, and there are certain things you can figure out. If a drug is excreted by the kidneys, it is easy to conclude that people with poor kidney function will tend to accumulate the drug. So one of the things you would ordinarily do for a drug excreted by the kidneys is find out what kind of dosage adjustment you need to make to get the right blood levels. That is, in the words we're using, figuring out what the effect of renal function or altered rental function is on the pharmacokinetics of the drug.

There are a number of things you can figure out. The difficulty is there is so many possible things that can influence pharmacokinetics of the drug that it's hard to anticipate them all. So what we proposed was a screening procedure. The screening procedure is very simple. You take essentially all of the patients in phase three of the clinical trials, which would number a thousand or more, and you let them get to a steady state so that the blood concentrations aren't changing, and then you find out what the blood concentration is on one or two occasions.

If there is something in a particular person that causes him to accumulate the drug, he will have a higher blood level and you will detect it. If you apply intelligent analyses, you will be able to see whether there is something about a particular group of patients that makes them accumulate the drug.

For example, you might discover that all the patients who are on some concomitant therapy, like Quinidine, an anti-arrhythmic drug, tend to have higher blood levels than all the people who don't. Now, that may tell you something right off the bat, that there's an interaction with Quinidine, or it may tell you you may need to do a better study to refine this.

You can carry out similar analyses of age, of ultra rental function of the presence of hepatic disease and so on. The virtue of all this is that you don't have to be smart. You just have to do it. You don't have to figure it out. The screen will tell you that there's something there.

It was controversial because it was a little bit novel, and there was some concern that there would be findings that would emerge whose interpretation might be obscured, that might lead us to say "oh, my goodness, that's just terrible; we can't approve a drug like that." So we needed to spend some time persuading people that this was a novel kind of data that we would be getting and that we would interpret intelligently and cautiously, and that it was mostly a matter that would affect drug labeling and we didn't have a bias that said drugs with certain properties would either rise or fall on this.

There has been some years of discussion of this. A subcommittee of the American Society for Clinical Pharmacology and Therapeutics has been considering this repeatedly and recently produced a document that said this seems like a good idea. It's not the only way to find out about how pharmacokinetics are altered in people, but it is a very good one. That makes me feel more comfortable about putting it in the ultimate guideline. So I still think it's a good idea.

What we have discovered in our review of the drugs approved over the last year is that virtually all companies are carrying out a pharmacokinetic study in older patients, which was very unusual, say, 5 years ago. But I don't see a whole lot of use of the pharmacokinetic screen. I would like to see more use of that because I think it's promising.

Dr. YOUNG. I think that's a good indication of how the process works with a function of time. Had we put the guideline out earlier, we would not have had this pharmacokinetic screen in it. It was just really in 1988 that the committee of the Society really endorsed these clinical pharmacokinetic guidelines, so it's a very dynamic process and we're trying to get as much done by discussion and persuasion and then finally capture it all in the guidelines. So the guideline will be a monument to what has already been done, and a codification of what has already been done, not breaking new ground.

Mr. DOWNEY. Can you deal with the question that I had asked Mr. Kusserow about education in medical schools, training, with respect to pharmacology, and also geriatric training?

Dr. YOUNG. There are two parts to the question and I would like to discuss each of them separately.

In my opinion, having spent a quarter of a century in medical education, there is less of a focus on basic science than I would like to see. The pharmacology courses that are provided in medical schools now usually are less than 100 hours and, not very frequently, are accompanied by detailed laboratory studies, so that we don't see the physician necessarily exposed to pharmacokinetic data and the analysis thereof. I worry, with a decrease in laboratory studies in medical schools, that at the time physicians are learning first about drugs, they may not be present.

The second part of medical education is at the graduate level. There, for all physicians not going into deep specialties, such as surgery, in my opinion, there should be a consideration at least of a core curriculum in clinical pharmaceutics, and I would even put it into the surgical subspecialties as well. For the physician, the single most important therapeutic regime is the use of medicine. I have not seen yet to my satisfaction, as a dean in one of the 13 schools in the State that we both came from, the type of education in medicinal drugs that I would like to see.

Now, then, superimposed on that is the specialty training in geriatrics. Here we are seeing an increased understanding. When Dr. Williams and I first started the program in Rochester, there was hardly one trainee a year that was going into geriatric medicine. We're seeing an increase not only in our medical center but other medical centers. That is a positive sign. But if you build specialization on top of a flimsy base of training in pharmacology and clinical pharmacology, I think it's unsound. Thus, I have been working with the Institute of Medicine and other organizations to try to point out the need for training in pharmacology, clinical pharmacology, and clinical therapeutics, and we're trying to develop the FDA into a national center for therapeutics, both drugs and devices, so that we can contribute in all phases of that pyramid. We contribute through the proper labeling. But Alex works with consumers and we work through a number of consumer programs—and I will introduce for the record his report that describes what we've done since the early Eighties on working with consumers. Dr. Stewart Nightingale works on informing the patients' representative, the physician, and we meet with medical health providers on a quarterly basis as well. We put out the FDA bulletin; we put articles out monthly in JAMA and other journals to try to focus on good therapeutics.

[See Appendix 2, p. 435 for report]

Dr. YOUNG. I think the final thing that I would say, that you also asked Mr. Kusserow regarding the system, is that we have a great concern, as he does, that the system is set up right for gathering adverse reactions for the elderly. We feel that this is a golden opportunity to look at a good system to gather good data, and I share his fear that it may be implemented before it's designed properly and that would be a deep shame.

Mr. DOWNEY. I want to let the other subcommittee members ask questions. I am going to come back to this question I asked you, because I'm pleased with your interest, but I'm not sure that I heard a specific answer to my question, which is—let me ask it again briefly.

We have enormous authority over medical school reimbursement and a whole variety of things. There are many ways we could suggest that medical schools do more in the areas that you suggested and provide more in the way of geriatric training. What I would like you to think about—and you don't have to answer me here, but either for the record or at some other point—is what else should we be doing to require that it happen. I understand we could sit around and be very polite with one another and say it's difficult and complicated. Yes, I hear it's very difficult and complicated, but these are bright young men and women and these are professionals. We can, as a Congress here, say look, we just want you to know more about these things. We spend a lot of money, we waste a lot of money. We are very concerned that the population is growing older, faster, and that the needs of our medical schools, which we provide an enormous amount of money to, frankly are not moving as quickly as we would like.

So what we would ask from you is maybe we can rethink this in maybe a more private setting of how we go back to the medical schools to urge them to do this in a bit more timely fashion, maybe using as a model some medical schools that already do a fine job here.

Dr. YOUNG. I would be delighted, after the other questions. I appreciate you deferring to your other colleagues. Then I will come right back and answer that and then provide additional information for the record.

Mrs. SAIKI. Can I ask one question on that point?

Mr. DOWNEY. Certainly.

Mrs. SAIKI. Have there been any efforts to gather data from the physicians themselves? I mean, physicians must feel very frustrated with the array of new drugs that come on the market on a monthly basis. There are people who work for the pharmaceutical houses who visit them in their offices to try to explain the pros and cons on the use of these drugs.

I think it's totally inadequate to just make a blanket statement. I'm not condemning anyone, but overall, I would say they're not as well trained as they could be. So physicians who deal with the elderly must be expressing some concern and frustration with all of this, the fact that perhaps they don't have enough training in medical school, that the pharmaceutical houses maybe do not provide enough information, or that, maybe, they don't have a gathering of information amongst themselves as colleagues.

Aren't they speaking up through their medical associations? Couldn't they be harnessed, so that it wouldn't be Congress imposing on medical schools the need for this training, rather than it come from the grass roots?

Dr. YOUNG. You're absolutely correct. I think the article that would be most helpful is the one that I mentioned on medical education response to the 20th century's success story, which essentially says that, as we become more successful, we made a major problem—the population over 75 is growing. It goes on to say that researchers found that by 1990, between 900 and 1,600 geritricians and 400 geriopsychiatrists would be needed to adequately staff the Nation's medical schools—that's medical schools alone—and about 8,000 full-time equivalents would be required to care for people over 75 years of age. The report goes on to describe what is present and what's missing.

One of the biggest frustrations I think—and Dr. Williams can provide further information as director of the National Institute on Aging—is the need to get geriatric training programs or centers of aging in most of the medical schools. I think the medical schools are responding. I would sort of like to use, as you implied, a carrot rather than the stick approach, and to stimulate these programs. I think it can be done and I will provide some detailed answers for the record of good models that have begun to focus on this. I would like to also provide some things that FDA is going to work with such organizations.

Mrs. SAIKI. Just to follow up, Mr. Chairman, isn't there also a means of harnessing the tremendous effort of the medical associations or the academies, the professional organizations—

Dr. YOUNG. Yes.

Mrs. SAIKI. {Continuing] so that the physician who practices internal medicine, for instance, who is not a geriatric specialist, who deals with the initial case more often than not—these people out there must feel that the gathering of information of this nature and pooling it and studying it from their level would be helpful.

Isn't there some way to harness that?

Dr. Young. Yes, there is. One of the things I have had the opportunity to do is meet with a number of the professional individuals in this arena. There is a growing concern that we develop a national consensus that would review not only the reimbursements, such as Medicare and Medicaid, but really what are the best national policies for developing health care for the aging population. This includes the whole aspect of home care, particularly in those terminal years. I will share something just a little bit because to me it was very impressive.

I've had the chance to help a couple of individuals die at home. Three years ago my bother and I helped my mother die at home. My brother was a minister in Pennsylvania and we selected his home for the home care for my mother as she was dying from cancer. My wife went up during the week. She's a nurse. I would go up on the weekends. We had our home support in our own home.

I think one of the things I would like to see come out of that is how we can support the elderly people with terminal illnesses in homes. We have made death a sanitized form of incarceration, where we put people in nursing homes and in hospitals, depriving them of being around their loved ones.

I was taking my mother's pulse when her last beat stopped. We were able to pray, to take her to the "valley of the shadow of death", not walk through it with her, but all of the family was there—my niece, my brother, his wife, my wife. Death occurred with dignity.

Whatever national approach we bring forward, if we don't focus on death with dignity, I believe we will have failed the American people and failed them badly. So I would be delighted to provide technical support for you on this. I feel very strongly about it. I think the time is now to look at not only reimbursement, not only medicine, but how we're going to help, each of us, as we grow older, to have the most productive life that we can, and that terminal illnesses have the most dignified death that's possible.

Mr. Downey. Ms. Snowe.

Ms. Snowe. Thank you, Mr. Chairman.

Dr. Young, getting back to the guidelines for a moment, normally when guidelines are issued, it is generally to require every group to perform a certain function uniformly. In this instance, the drug manufacturers can voluntarily use elderly in their clinical studies; is that right? So it's not a question of the fact that they have to do it. They can do it if they choose to do it.

Dr. Young. The drug application has to be approved by the Food and Drug Administration. If the Food and Drug Administration advises strongly that it is essential to do drug analyses in the relevant population and specifies what is required for drugs for the elderly, I want you to know, though, that is voluntary compliance. That has about the strongest "stick" that you can imagine.

Now, if you went to a regulation, which is the other way to go, we find that a regulatory response—just as if we knew the regulation was going to be required today—to get that into the force of regulation, you are looking at a 3-4 year process, just by the legal things that we have to do, possibly an advance notice of rulemaking, a proposed notice of rulemaking, a final rule, all of the comments in between.

We would prefer to put this into a clinical guideline after negotiating it and then essentially require, by the way we review the drugs, that these population criteria are met.

Ms. Snowe. I'm not saying you wouldn't have a certain amount of diversions because the Congress mandates over time, but this has been approximately 6 years. Last June you did indicate to Senator Melcher, of the Special Committee on Aging, that in a few months you would have a draft guideline. It is now almost a year and now you're saying another few months.

I guess the point is, when can we expect those guidelines, and do you find that we should formally publish them?

Dr. Young. First of all, I don't want to be snide, but I think each of us have responsibilities that we don't quite meet. The Congress of the United States responsibility is to balance the budget and we have not had a balanced budget for a while.

Ms. Snowe. I understand that. That's not—

Dr. Young. Let me come back to the direct point.

Ms. Snowe. Let's focus on these guidelines. It's been 6 years. Now, have you come back to Congress and maybe asked for additional resources? Maybe that's the problem. But I think at some point we have to make a determination on whether or not you're going to formally publish those guidelines, because without that formality, the drug manufacturers don't necessarily have to comply.

Dr. Young. Surely. First of all, the guidelines will be formally published, and they're being negotiated, as I said. Bob has finished the review and it will come out. I expect them to be out soon. I can't predict the exact time. I don't want to be misleading you in any way. But I do truly expect them to be out soon.

Now, the other point is, once we put in the 1988 reg, that you had to study these populations, the industry is already moving. When we get the guideline out, we will have an accomplishment, a monument to codification. But there will probably be a very small modification of behavior because that already will be in place.

Ms. Snowe. Why not publish them as you go along?

Dr. Young. We have, in fact, done that. The NDA review, for example, which occurred on my watch, came out at about 1985. Thirteen guidelines came out associated with that. Some dealt with chemistry, others deal with the other forms, and we publish those guidelines all along, the latest of which was the one that Bob talked about on clinical and statistical methods.

Now, we want to put a capstone on that which we look at as the guidelines. Frequently, when we set out on a particular direction, we would say wow, the guidelines look like they're going to be the best way to handle it. But as we go through, we publish pieces upon pieces upon pieces, and that's exactly what we did by putting this particular guideline out earlier, and now, by having a regulation in place that will require a portion in the Physicians Desk Reference that will focus on geriatric guidance.

Ms. Snowe. What percentage of drugs are currently being voluntarily tested on the elderly?

Dr. Young. We did that, and I want to ask Bob to respond directly. But those are the figures that I gave earlier. In 1988, as we have looked at it, 7 out of 8 of the drugs that we reviewed in detail had pharmacokinetic data related to the elderly. The bulk of the drugs that we are seeing in '88 so far and have analyzed so far have that. But, Bob, would you give the exact figures on it?

Dr. Temple. Yes. It is worth reminding people that the idea that drugs are studied in healthy young people and given to older sick people hasn't been true for a long time, if, indeed, it ever was. In 1983, when we reviewed just a sample of 12 drugs available, most of them had extensive exposure in people over 60. That doesn't mean they had extensive exposure in people over 90, which is a different problem. But the drugs are worked up in those people for a very simple reason: it is difficult to find patients to include in clinical trials. If you exclude people over 60, you just don't find a lot of people with angina. So the idea that those patients are excluded isn't correct.

Let me tell you very briefly of our most recent survey. It isn't quite complete. We just tried to get data on all of the drugs approved in 1988, an unselected group. I have something on 15 of them.

For three there won't be very much because they were orphan drugs, for unusual cancers or something like that, so there is not a lot of data. But I have information on 11 of the drugs that were approved and most of the ones that are relevant.

There is extensive use in all of them, of populations that include the elderly. The lowest percentage was 18 percent, and that was over 400 patients. Most of them run about 30 percent of the population that was studied over 60. A fair fraction is also over 70, but you don't find a great many people over 80. That persists as being true.

What is equally important—Let me just backtrack. Three of the drugs are single dose drugs that are given to people for radio-contrast materials, so that although they were widely used in older populations, some of these other things I'm going to describe weren't relevant.

Of the eight sort of general use drugs, seven of them had specific pharmacokinetic studies done in an older population. Six of them had formal studies of the effect of kidney disease, six had a formal analysis of either side effects or effectiveness by age, as we have requested in the guideline. And four of the eight had pharmacokinetic studies looking at the effects of hepatic disease. So there is very substantial response to the discussion paper of 1983.

It is worth mentioning that that was intended in 1983, to be a discussion paper. We felt that there was more to learn about what to do before we were ready to propose a guideline. So I'm not sure it's 6 years we've been waiting, although I have been certainly promising to finish the thing off for a couple of years.

To me, the progress is enormous. In fact, drugs are studied in older patients. The guideline will urge people to try to study the frail elderly, the so-called—you know, they're either very old people over 80 or people with complex disease. I'm not sure yet how successful we'll be in that case. You could almost ask whether it's even fair to that population to put a new drug into a frail patient, one that you don't know a great deal about. So that's a formidable problem, the answer to which is not so clear.

But what our approach will be is to try to define all the things that might make you want to adjust dosage in anybody, and all of that information will be disproportionately valuable to the elderly because they have more of those things—renal disease, liver disease, other drugs and other diseases—than younger people do. So to the extent that you learn how to individualize therapy, it will help the elderly disproportionately. That's the thrust of the interest in pharmacokinetics.

Ms. SNOWE. Do you have documentation of how standards are applied by the drug manufacturers in these clinical studies?

Dr. TEMPLE. I'm not sure I understand the question.

Ms. SNOWE. Do you know how they perform these studies? Are they done uniformly? Are there certain standards that all drug manufacturers use, using the elderly in these test studies? Are they stringent tests or less stringent tests?

Dr. TEMPLE. Again, it was common in the past to exclude patients over a certain age. That is, the protocol for the study would say nobody over 65. You don't see that any more. Patients are now entered if they meet the entry criteria. So that is a specific change that probably occurred over the last 10 years.

Dr. YOUNG. Possibly I can help on that for you.

The focus really depends on the drug, so that, depending on what drug would be used, there might be different standards. There would be different standards for cardio-vascular drugs, different standards for drugs dealing with hypertension. As each of these go through, what we try to do is, for drugs for the desperately ill, to have a conference with the sponsor at the end of phase one, after they have done the safety data, and then work out with them what is required for the definitive test, if it's going to be only a phase two study. If there is all three phases, we urge through these guidelines that they come in and discuss with the agency what is required before the final clinical trial is started. That gives us a chance to really tailor the particular kinds of things that people should study to the drug.

I think one of the misinterpretations, in listening to the questions, is the fact that the guidelines are really what's important, and then the NDA comes in and we evaluate it. As I have learned in the past 5 years, particularly as we have been trying to accelerate drugs to desperately ill people with AIDS, people with cancer, the most important thing to do is to bring the sponsor in early and then have that sponsor work with the Food and Drug Administration and talk about what is necessary to get the right results. That gives us a chance to introduce some of these suggestions which in many instances require populations.

Just recently, we had a conversation with a particular drug company trying to get a drug for AIDS. We looked at that and said that population won't work, you really ought to try this population. So we do an awful lot of that in guidance in the clinical development stage.

Ms. SNOWE. As a result of these studies, have you found that the drug manufacturers use the information on the studies for drug labeling purposes or for information use instructions?

Dr. Young. Yes, we have been pleased with that. Because one of the things that FDA does when it looks at the NDA is to develop the proper labeling requirements. They have to negotiate at the time of approval exactly what the label should say and exactly what sort of contraindications should be in it. Now we're putting forward a regulation, as I mentioned, which is in General Counsel, that will require a prominent and visible display of some of the issues dealing with geriatric use. We feel that's very important.

Ms. Snowe. In the Inspector General's report, it was indicated that only 17 of the 200 most commonly prescribed drugs give specific geriatric dosage instructions, and specific information on adverse reactions is provided for only 18 within that same group of medications. It goes on to say that among the 24 most commonly prescribed drugs for elderly, only three product labels cite geriatric patients under adverse reactions and only five mention geriatrics under dosage and administration.

Dr. Young. We have discussed that. As I said, there is not a lack of concurrence with our approach. Now, remember, that was a tentative report and he was looking at different parts of the label. One of the things that I mentioned in our regulation that is so important—and here I support strongly your concept of standards—is to have a separate spot where you can pull these out. If you look at the Physicians Desk Reference on labeling, the print is terribly fine and it goes on sometimes for two or three pages on a drug. What we reason now is that we want a very prominent area that talks about geriatric use. That we will put out as a regulation, not as a guideline, and that's a very important difference between how we work with guidelines and how we work with regulations.

Ms. Snowe. Does FDA take any punitive actions against a company or researcher if they have violated the rights of an elderly person who is the subject of that research?

Dr. Young. Yes, we can. We can disqualify investigators. A short time ago there was an investigator that was doing fraudulent research, I believe in New Jersey. He is now spending many years in the penitentiary. We also have gone after executives of pharmaceutical companies—I won't particularly mention the names, just as I didn't the physicians—but there were some cases a while ago.

We have continued to look at labeling. When there was a drug a short time ago that came out with inappropriate advertisements that was misleading, we brought that to the attention of the company very vigorously. That labeling was removed. The FDA tries to keep an oversight and keep standard practices in the marketplace. We are particularly committed to strengthening this geriatric labeling. We're a bit embarrassed. It looks like 6 years, but really there has been an awful lot of consensus development. The way we best do business, in the Administrative Council of the United States that I serve on—it's about 100 lawyers, and I'm one of the two nonlawyers, a "token doc"—tried to point out that if we do have a negotiation of guidelines, we're far better off than putting out a regulation or a guideline that nobody supports and then go through years of litigation. We're trying to negotiate this as we go for it.

I have something that was just given to me, that on the inspections for cause, from 1977 to 1988, we have had 443 inspections and

44 disqualifications, 21 through the regulatory process and 23 through consent agreement, and 23 of these have agreed to some degree of restriction. So that we do have more teeth in the capability for following compliance on clinical investigation and the certification of the studies being correct than almost any other organization looking at science.

For example, diverting your question but giving you a good example of this, when we approved AZT, we looked at every one of the single studies and, in fact, where there was one study where we had a question, we called in all of the clinical investigators and the manufacturer to go over this. I chaired that meeting and asked those questions as to whether or not that drug could be really approved in that study. We had no problem with the other 11 studies, but we wanted to deal with the data.

So the FDA usually will take an enormous amount of information as it goes through. The average new drug application is 100,000 pages. It includes all of the clinical data. In the case of AZT, that was 20 linear feet. I have now learned that 175 pages equals 1 linear inch. We have had to go through many of these linear inches trying to be sure that the doc doing the test is honest and the company reporting the results is reporting it honestly. I would say that for the vast, vast majority of manufacturers and the vast, vast majority of clinical investigators, I am pleased to say that these are reported honestly, fairly, and we can get good cooperation in analyzing these new drug applications.

Ms. SNOWE. Thank you very much, Dr. Young.

Thank you, Mr. Chairman.

Mr. DOWNEY. Doctor, we can continue the process of discussing the application of pharmacological information and geriatrics at another time for universities. We have other panelists that we've made some commitments to and need to get them on. I want to be able to do that.

But I would like to have us continue with this—

Dr. YOUNG. I would be delighted to do so, just delighted to do so. It's an area of great interest.

Mr. DOWNEY. It is to me, as well. Dr. Young.

Dr. YOUNG. Thank you for having the hearing and having us here.

Mr. DOWNEY. My pleasure. Thank you.

Our first panel is comprised of Dr. T. Franklin Williams, Director of the National Institute on Aging; Helene Levens Lipton, Associate Professor of Social Pharmacy, School of Pharmacy, University of California at San Francisco, and coauthor of "Drugs and the Elderly: Clinical, Social and Policy Perspectives"; and Dr. Monroe T. Gilmour, AARP Board of Directors.

Dr. Williams, it is an honor and a pleasure to have you here. We will ask you to proceed first.

PANEL ONE, CONSISTING OF: T. FRANKLIN WILLIAMS, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES; HELENE LEVENS LIPTON, PH.D., ASSOCIATE PROFESSOR, DIVISION OF CLINICAL PHARMACY, SCHOOL OF PHARMACY, AND SENIOR RESEARCH ASSOCIATE AND CORE FACULTY MEMBER, INSTITUTE FOR HEALTH POLICY STUDIES, SCHOOL OF MEDICINE, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO; AND MONROE GILMOUR, M.D., MEMBER, AMERICAN ASSCOATION OF RETIRED PERSONS BOARD OF DIRECTORS

STATEMENT OF T. FRANKLIN WILLIAMS

Dr. Williams. Thank you very much, Mr. Chairman. I am Dr. T. Franklin Williams, the Director of the National Institute on Aging. I certainly welcome this opportunity to participate in testimony on the use of medications in older persons.

In my judgment, it is important to consider the use of medications in the context of our best knowledge about aging based on the most recent research. I want to just touch briefly on a couple of points here. First of all, there is the need to distinguish what we refer to as "intrinsic aging" from extrinsic factors in older persons, such as different lifestyles, environmental exposure or diseases or the effects of drugs, which in turn modify the response of people to new drugs. In fact, these extrinsic factors account for most of the changes seen in older persons which in the past have been attributed to aging itself. Given good health practices and good fortune in not having some of these diseases, we find in our best studies that most organ functions are maintained very well into late years and would not account for much of the changes we attribute to aging. Whenever we do see changes, we should look for some potentially modifiable factors such as lifestyle or diseases. I can give more detailed data on a number of these backup evidences.

Second, there is a need to recognize the immense variability between older people. Older persons are more different from each other than they are different as a group from younger persons. In our institute, I don't allow the term "the elderly" to be used because that implies a group which is certainly not true. All older people are different, and this means, in terms of medications, we need to have highly individual decisions made about the use of drugs.

Finally, in terms of background, older people have considerable potential for restoration of function and independence of living, and this should always be our goal in treatment which certainly justifies the appropriate use of medications as well as active attention to improving other factors.

With these background things, I would just like to take a few moments to point out what I would consider some of the major challenges and opportunities for further research and development, specifically regarding medications, that may benefit older people.

To start with, one of the most important, I believe, is that we have the opportunity to develop and use replacement hormones and immunological preparations which can replace or modify some of the things that are lost genetically with aging, such as the effects of menopause on bone loss, the effects of immune changes that are common in aging. We have potential ways to replace or correct some of the changes that do go on with aging, and that also includes some of the changes that go on in the structural proteins of the body, the stiffening of collagen and other connective tissues. There are potential leads now in research that would suggest ways that we may modify some of these, if you will, intrinsic aging changes.

When we turn to some of the major disease conditions in older people, certainly Alzheimer's disease is the greatest challenge facing us today and, quantitatively, by far the largest epidemic in our whole society. Here we have a number of potentials for very promising interventions, including the potential use of nerve growth factors to stimulate regeneration or replacement of nerve loss in the process of Alzheimer's disease, and there are other clues to other ways that we may be able to interfere and halt this disease.

In addition, as I am sure you are aware, we are conducting a large clinical trial on the drug THA, or tetrahydroaminoatrodine, which probably will offer some relief of some of the symptoms in Alzheimer's disease, although it doesn't reverse the process. That is not clear yet. We will have the results of this double trial by autumn and will really know then and have some idea of its efficacy and safety. In addition to that drug, there are about 10 or 15 other drugs awaiting further trials that probably warrant testing for relief of symptoms in Alheimer's disease. So here is an area where advances in the use of medications and compounds like growth factors can make an enormous difference, if successful.

Another example is depression in older people, very often overlooked, and in most instances it is a treatable condition.

In areas of physical frailties, such as osteoporosis—I have already referred to that—but also osteoarthritis, in addition to a number of advances being made in medications in these fields, there is also the possibilities of growth factors here that may help restore cartilage or restore bone. I hold these out as reasonable prospects for further development of targeted interventions for older people.

I want to just point out that cardiovascular disease and cancers remain the largest killers in older people, and much effort is certainly continuing on medications in both of these fields and I won't dwell on them further at this time.

Finally, I would just support what has already been said by Mr. Kusserow and Dr. Young—and I know it comes up in other comments among my fellow panelists—that we do need to move on opportunities to improve the prescribing of drugs effectively and in testing drugs in older people, drugs that are going to be used in older people, and in particular, trying to find out how we can test them in the complex settings in which older people exist. That's the real challenge, and Dr. Temple addressed this to some degree. But I think this continues to be a very important issue.

I just want to end my comments and would be very happy to try to address other questions in more detail. I would also say, as others have pointed out, that we certainly need more education and training by physicians and all health professionals in the proper use of medications for older people. Our Institute is engaged in this and we support research, career awards and training awards and a number of research grants supporting this field. We have supported special conferences on pharmacology and aging, along with the Food and Drug Administration, the American Society for Clinical Pharmaceutics, and we are also working with the Institute of Medicine on a special symposium next month. We have about $6 million invested in research on pharmacology and aging, and are inviting more applications with the intent of expanding this.

I would be glad to answer questions, Mr. Chairman.

[The prepared statement of Dr. T. Franklin Williams follows:]

STATEMENT BY

T. FRANKLIN WILLIAMS, M.D.
DIRECTOR

NATIONAL INSTITUTE ON AGING
NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HUMAN SERVICES
OF THE
HOUSE SELECT COMMITTEE ON AGING

April 19, 1989

Mr. Chairman and members of the committee, I am Dr. T. Franklin Williams, Director of the National Institute on Aging, National Institutes of Health. I welcome this opportunity to participate in testimony on the use of medications by older persons.

In my judgment, it is important to consider the use of medications in older persons in the context of our best knowledge about aging, based on the most recent research. Three key points need to be made. First, there is the need to distinguish "intrinsic aging" from extrinsic factors which may affect older persons, such as different life styles, environmental exposures, diseases, and the effects of medications already being taken. These extrinsic factors account for most of the changes seen in older persons which, in the past, have been attributed to aging itself. Much recent research shows that, in the absence of disease and with reasonable life-style practices, most older people maintain very good functioning in most organ systems--heart, brain, and kidney, for example. For the most part, when we see changes or symptoms in older people we should look for potentially modifiable factors such as life style or diseases.

Second, there is the need to recognize the immense individual variability between older people. Older persons differ more from each other than they differ as a group from younger persons. This calls for highly individual decisions about use and dosage of medications.

Third, the potential for restoration of function and independence of living in older people should always be the goal of treatment, and clearly justifies the appropriate use of medications as well as active attention to improving lifestyle and environmental factors. For example, appropriate therapy for postural hypotension (a drop in blood pressure when standing, which causes dizziness and, occasionally, fainting in many older persons) not only corrects the blood pressure problem but also may allow an older person to maintain daily activities independently instead of needing supportive care. Thus appropriate drug therapy can increase an individual's independence and reduce his or her need for long term care.

Against this background, there are major challenges for further research and development aimed at prevention and treatment, including the use of medications, as well as appropriate use of those medications we already know about. Let me summarize some of these challenges and opportunities. We need to foster appropriate development and use of endocrine, hormonal and immunological preparations to replace or modify factors that do change with aging. For example, age-associated changes in immune responses in some older individuals may impair their resistance to infections, but are potentially correctable by new pharmacologic interventions. There is also the potential for modifying the aging processes that produce structural changes in body proteins. Such interventions have the potential for reducing cardiovascular disease and other damaging effects of the stiffening of these proteins.

In Alzheimer's disease (AD)--the greatest challenge facing us today in older people and quantitatively by far the largest epidemic in our aging society--there is the potential for very promising interventions, including the use of nerve growth factors to halt or reverse the degenerative changes in the brains of Alzheimer victims. In addition, it seems likely, although still to be proved, that drugs like THA (tetrahydroaminoacridine) will at least temporarily improve brain function and relieve symptoms. As you know, our Institute is currently carrying to completion a large, 17-site double-blind clinical trial of THA. We expect to be able to announce definitive results on both the safety and efficacy of this drug by early autumn. In addition, 10 to 15 other drugs appear likely to warrant testing for their value in AD. Conquering Alzheimer's disease is the highest priority of our Institute.

Depression is a problem often overlooked in older patients and is, in most instances, a treatable disorder with appropriate use of medications.

We also need to expand our knowledge and capabilities for relieving symptoms and improving function and independence in persons suffering from physical frailty due to osteoporosis, osteoarthritis and muscle weakness, including exploration of such possibilities as growth factors for cartilage, muscle, or bone.

Cardiovascular disease and various cancers continue to be the largest killers of older people. Thus research and interventions to prevent and treat these conditions continue to be of great importance. Much progress has been made in the control of hypertension and in minimizing the risks for coronary artery disease and strokes, but we can still go further. Certain malignancies are particularly common in older people, such as cancer of the colon, breast, and prostate, and present major challenges for new understanding and new pharmacological treatments.

Finally, there are certainly opportunities for improvements in the prescribing of medications as a part of achieving their desired benefits without hazardous or undesirable side-effects. We must have adequate testing in older people of drugs which are proposed for their use; and this must include testing in the face of complex combinations of diseases and multiple medications which are common in older people.

There is the need to know more about the side effects of medications as possibly contributing to some of the common problems seen in older persons, including falls, incontinence, and confusion. Several studies supported by NIA and others indicate that such side effects contribute to clinical problems of older persons in ways we did not previously appreciate. This opens up new possibilities for better prevention and treatment of these problems by better drug prescribing.

It is also important to learn more about nonpharmacologic alternatives to drug therapy for problems of older persons. Such approaches may reduce many of the adverse reactions and costs associated with drug treatment. For example, NIA in collaboration with the National Center for Nursing Research has tested behavioral therapies for urinary incontinence for older persons. These clinical trials have shown that these approaches are effective for many older persons, sparing many the risks and costs of drug treatment.

It is very important to learn more about the long-term effects of chronically administered medications on all aspects of the lives of older people who are taking them. An example of a careful approach to this issue is found in the large clinical trial of treatment of systolic hypertension in older persons being conducted by the National Heart, Lung and Blood Institute and the National Institute on Aging, in which the drugs being used are being monitored for their possible effects on mood, on overall functioning (both physical and cognitive), as well as on blood pressure itself and on end-points such as the occurrence of strokes. The importance of such a comprehensive approach is illustrated by the fact that such a study allows us to determine whether controlling systolic hypertension will also reduce the risk of multi-infarct dementia, which is associated with strokes and is the second most common type of dementia. Another study, at an NIA-supported Teaching Nursing Home (TNH) in Philadelphia is taking a similarly comprehensive approach to the risks and benefits of antimicrobial treatment for chronic urinary tract infection.

There is clearly the need for more adequate education and training of physicians and all health professionals in the proper use of medications in older persons, including raising their sensitivity to the risks of overuse. Studies have shown that such training can markedly lessen unnecessary prescribing of medications such as tranquilizers. Further studies are needed to determine the full potential of such approaches for drug treatment of older persons.

More scientists are needed in the fields of clinical pharmacology and related research in aging. Our Institute is working to increase both the research being conducted on pharmacology in aging and the training of more academic leaders in this field. We have sponsored symposia with the Food and Drug Administration, the Merck Foundation, and the American Society for Clinical Pharmacology and Therapeutics; and we are working with the Institute of Medicine on a special symposium on Drugs in Older Persons to be held May 24 and 25 of this year. A major focus of this symposium will be ways of improving drug utilization review in large systems such as Medicare/Medicaid and using the information from utilization review for further improvements in therapy.

NIA currently supports $6 million per year of pharmacology-related research and will issue a request for further research proposals in this area later this year. This request will solicit projects to test approaches to improve efficacy and reduce adverse reactions of drug prescribing for older persons.

I will be pleased to answer any questions the Committee may have.

Mr. DOWNEY. Thank you, Dr. Williams. We will hear from the remaining members of the panel before we address questions.

Dr. Lipton.

STATEMENT OF HELENE LEVENS LIPTON

Dr. LIPTON. Good afternoon, Mr. Downey.

I would like to focus my discussion this morning on rational drug use among the elderly, which as I see it, depends on three critical factors: patient is safe and effective drug use, physician's prescribing with cost as well as quality in mind, and the use of quality assurance mechanisms, sometimes involving other health professionals, to assure that each of these goals of rational drug taking and drug giving is met. In my testimony I will briefly describe each of these three issues.

As we have already heard this morning, a major area of medication misuse among our Nation's elderly living in the community is less than safe and effective drug use, often referred to as noncompliance. Noncompliance involves a patient's inability and/or unwillingness to take their prescriptions in accordance with their physician's directions.

Noncompliance can take many forms. Most often among our elderly, it involves underuse of prescribed drugs, but it also can appear in the form of overuse or inappropriate use. It can be intentional or unintentional. But whatever its form or intent, one thing is abundantly clear: noncompliance among our noninstitutionalized elderly is widespread, estimated at about 40 percent.

The elderly are particularly vulnerable to noncompliance because many of the risk factors are characteristic of elderly populations: multiple drug regimen, long duration of drug treatment, physical and mental impairments, social isolation, inadequate knowledge of the drug regimen, and less than optimum communication between health professionals taking care of our Nation's elderly and the elderly themselves.

I think it is important to note that less than safe and effective drug use can have enormous clinical and economic consequences. Some analysts suggest that about 10 percent of hospital admissions result from poor patient compliance and that geriatric patients are particularly at risk. Other outcomes associated with noncompliance can be equally serious—impaired quality of life, compromised health status, and needless death. That's the bad news.

The good news is we do know a great deal about behavioral changed strategies that can prevent, detect and great noncompliance. We know, for example, that specific and detailed drug information must be provided. We know that oral information must be supplemented by written information, such as patient package inserts. We know that specific communications strategies need to be used by health professionals to maintain patients' motivation to take their medications and we know that patients' drug use needs to be monitored over time.

We also can deduce that these strategies are not being taught in the overwhelming number of our Nation's medical schools. Some of our witnesses this morning have suggested the need to integrate principles of geratric pharmacotherapy and pharmacology into our medical school curricula. I concur with these recommendations, but I should like to add that the incorporation of behavioral change strategies to enhance the safety and efficacy with which our Nation's elderly take their drugs is another vitally needed area of curricular change.

Most experts agree that there is evidence of widespread prescribing patterns that are inappropriate for older adults, and some of the studies cited this morning do identify specific drugs that are implicated in inappropriate use. But what we lack are systematic empirical studies of the magnitude and nature of the prescribing problem in noninstitutional settings.

Much has been made about the incidence of drug-drug interactions, but I submit that that's only one component of the drug prescribing problem for our Nation's elderly. If the use of a drug in a given study is considered inappropriate, did the problem concern the dosage of the drug, the duration of drug therapy, the therapeutic duplication, a drug allergy, inappropriate selection of a drug, or was the problem a true adverse drug reaction, which by definition is not preventable? Needed are large-scale epidemiologic studies of specific patterns of inappropriate prescribing and, of equal importance, their relationships to hard, clinical outcomes.

We know, and it has been cited this morning, that the elderly, for example, are particularly vulnerable to drug-induced hospitalizations. But we don't know precisely how vulnerable they actually are. Estimates vary widely, from 10 to 31 percent, due to serious problems with available studies. So a critically important question becomes: what kind of specific drug therapy problems lead to adverse outcomes like drug-induced hospitalizations. Given the current, well-deserved emphasis on rigorous evaluation of health care outcomes, it becomes extremely important to develop tools to assess the incidence and characteristics of drug-related problems leading to adverse outcomes, and it becomes equally important to determine which of these problems are preventable. I submit that this kind of information would be very critical, given the current passage of the Medicare Catastrophic Coverage Act.

Much has been said about the expanded role of today's highly-trained clinical pharmacist serving as drug therapy consultants to geriatric patients and their physicians. Indeed, today's clinical pharmacist can do a whole lot more than count and pour and lick and stick. But clinical pharmacists, studies have shown, can enhance the physician's drug therapy decisions and improve patient compliance, curtail drug costs, and reduce outpatient visits and hospitalizations. But in order to achieve these objectives, community pharmacists need clinical data, particularly diagnostic information, and a complete record of the patient's drug regimen.

The proposed electronic claims processing database being developed by pharmacists participating in Medicare's catastrophic coverage program need to contain more than simple eligibility and deductible status information in order for community pharmacists to be able to use their skills. I think access to this kind of clinical and diagnostic information will be essential, or we will not have successful quality assurance mechanisms that the Medicare catastrophic coverage hopes will be achieved.

Clinical pharmacists in hospital settings—my final note—can also play a critical role in community-based geriatric care. More and more hospitals in our country are developing or are aligned with ambulatory care clinics, and because they are part of the hospital team, hospital-based pharmacists have more direct access than do community pharmacists to physicians, to patients, and to pertinent clinical and diagnostic data. As a result, this particular group of pharmacists should not be ignored in our potential thinking in the context of the current legislation.

There are available current models and demonstration projects that are using hospital-based clinical pharmacists and other innovative approaches using clinical pharmacists in community settings. These are major demonstration projects that are being conducted across our country. We need to look at the results of these evaluation efforts and, if they are successful, we need to develop innovative approaches to implement them, especially in the context of the Medicare Catastrophic Coverage Act, which has as its major goal improvement of the quality of drug therapy.

I have several other proposed recommendations, but not the time to explicate them. I would like to close by saying that if the proposed recommendations that I have discussed with you this afternoon—and hopefully we can discuss in greater detail later—are implemented, they have the ability to improve the quality and economy of drug therapy for our Nation's elderly, and the Medicare program's cost containment savings will be realized as well. Our Nation's elders, and our society, deserve no less.

Thank you.

[The prepared statement of Helene Levens Lipton follows:]

Statement by

Helene Levens Lipton, Ph.D.

before the

Subcommittee on Human Services

Select Committee on Aging

U.S. House of Representatives

on

Drug Misuse Among the Elderly and Its Impact on Community Based Care

April 19, 1989

Dr. Lipton is Associate Professor, Division of Clinical Pharmacy, School of Pharmacy, and Senior Research Associate and Core Faculty Member, Institute for Health Policy Studies, School of Medicine, University of California, San Francisco.

Drug Misuse Among the Elderly and Its Impact on Community Based Care

I. Introduction

When we think of the "drug problem" in the United States, the image of the elderly is not the first to come to mind. Yet the use and misuse of prescription drugs by older people is a subject of increasing concern. The consumption of prescription and nonprescription drugs in our society is practically universal. There is a common perception that there is "a pill for every ill." Nowhere is the use--and misuse--of medications more prevalent than in our elderly population.

The purpose of this testimony is threefold: to describe patterns of geriatric drug use and misuse in community settings; to analyze the economics of drug use among the elderly; and to propose prescriptions for change.

II. Geriatric Drug Use

How Many Prescriptions Do The Elderly Receive?

Data consistently indicate that the elderly use more drugs than any other age group. Several surveys have found that the elderly receive twice as many prescriptions per year than does the general population. For example, a national household survey sponsored by NCHSR found that the population as a whole took 7.5 prescriptions per year, in 1977, but those 65 years of age and over received 14 prescriptions per year. More recent figures project that the elderly living in the community will receive 18 prescriptions this year (Waldo 1987). Even within the elderly population itself, drug use goes up with age. In a national household survey of elderly persons living in the community--the

1980 National Medical Care Utilization and Expenditure Survey (NMCUES)--it was found that the number of prescription drugs used increased with age. Beneficiaries 65 to 69 years of age received an average of 10 prescriptions per year, whereas those 70 to 74 years received 12 prescriptions, and those 75 to 79 received 15 prescriptions. This trend, however, did not continue for those aged 80 and over, probably because of the high rate of institutionalization in this age group (LaVange & Silverman 1987).

The relationship between greater age and greater drug use reflects an inescapable fact-of life-for people over 65: 80 percent suffer from one or more chronic illnesses, such as heart disease, hypertension, or diabetes; and most of these diseases are controlled by long-term drug therapies.

What Types of Drugs Do the Noninstitutionalized Elderly Receive?

A 1980 survey done by the National Center for Health Statistics showed that the three categories from which most drugs were prescribed for the general population were central nervous system drugs (e.g., tranquilizers), antiinfective agents (basically antibiotics), and cardiovascular drugs. But a different picture emerged when drug use was examined by age and sex (Table 1). In male and female groups aged 65 and over, cardiovascular drugs (such as cardiac drugs and antihypertensive agents) and diuretics prevailed.

Additional data on drug use by the elderly living in the community are presented in Table 2. Here we see a list of drug categories most frequently prescribed for patients in various age groups in 1982. The most commonly prescribed drugs for persons aged 65 to 74 are antiarthritics, followed by cardiovascular drugs, (including beta-blockers, thiazide, and related diuretics). For persons 75 and over, digitalis is the drug most often prescribed. Cardiovascular drugs rank high in both surveys because of the prevalence of hypertension and heart disease in elderly populations, and the increased availability of drugs to treat hypertension, cardiac arrhythmias, and angina.

Interestingly, psychotropic drugs do not emerge as very strong contenders in either survey (Tables 1 and 2). The elderly living in the community are assumed to be heavy users of psychotropic drugs, but the majority, in fact, do not use these drugs. Use of minor tranquilizers is actually most common among persons 50 to 64, and seems to decline slightly beyond that age. Use of major tranquilizers is not clearly or consistently related to age at all. But use of hypnotics (sleeping pills) is most common among the elderly and is a subject of increasing concern.

Factors Affecting Geriatric Drug Use

What factors contribute to the widespread and increasing use of prescription drugs by the elderly? First, there is a broadening spectrum of safe and effective drugs from which physicians can choose. Second, physicians are often influenced in their prescribing habits by drug companies, primarily through professional sales representatives or "detail persons", who personally call on physicians. Third, the patient population is growing more medically sophisticated, and their demand for drugs affects physicians' decisions about drug use. Patients bring complaints to physicians and expect relief. Regular users of long-term, repeat prescriptions, most of whom are elderly, want to feel that their visit to the physician is worthwhile; as a result, physicians oblige with a prescription in about 80% of office visits.

III. Geriatric Drug Misuse

Drugs in an Aging Body. Many physicians do not recognize that drugs act differently in an aging body or that an aging body responds differently to drugs. Age-related changes in the body's mechanisms of drug distribution, metabolism, and excretion increase susceptibility to drug-related problems (Lamy 1980). As a result, while the geriatric population is most likely to benefit from modern-day therapeutics, it is also a population particularly at risk for adverse drug-related outcomes. Among all patients admitted to the hospital from the community, patients 65 years of age and older have the greatest admission rate (10 to 25 percent) for drug-induced symptoms (Hurwitz 1969; Caranosos et al., 1974; McKenney and Harrison, 1976; Levy et al., 1979; Bergman and Wiholm, 1981; Ives et al., 1987). More recent studies focussing on geriatric patients suggest that 10 to 31 percent of admissions are associated with drug-related problems (Williamson and Chopin 1980; Popplewell and Henschke 1982; Grymonpre et al., 1988). Drug-induced illnesses are associated with appreciable morbidity and mortality, as well as high costs estimated at $4.5 billion to $7 billion annually (Kusserow 1989).

The Dangers of Polypharmacy. A medication problem encountered by elderly patients involves polypharmacy, or the unnecessary, incorrect, or excessive use of medication. Polypharmacy can involve misuse of nonprescription drugs, of prescription drugs, or of both. Although the term "polypharmacy" is often used in a very broad sense, it can be defined so that it applies to specific problems among the elderly (Simonson 1984):

- Use of medications that have no apparent indication (e.g., prolonged use of sedative hypnotics for insomnia);
- Use of duplicate medications with similar or identical pharmacologic effects (e.g., use of two different sedative hypnotics prescribed by two different physicians, producing a "hangover" effect);

- concurrent use of drugs which can result in a drug-drug interaction (e.g., use of antacids with digoxin, thus decreasing absorption of digoxin);
- Use of medications that are inappropriate for a particular condition (e.g., use of a beta blocker such as propranolol for patients with heart failure, which can worsen the condition);
- Use of inappropriate dosages (e.g., excessive doses of the more potent diuretics, which can produce postural hypotension and precipitate falls in the frail elderly); and
- Use of drugs to treat adverse drug reactions, thus exacerbating the polypharmacy spiral (e.g., use of L-Dopa to treat Parkinson's-like side effects produced by major tranquilizers)

How widespread is the polypharmacy problem? Although we lack precise data regarding its magnitude, available studies suggest that excessive prescribing is widespread. Why? We have already mentioned that many physicians do not recognize the elderly patient's susceptibility to drug problems because of age-related changes in the body. Consequently, commonly used drugs such as digoxin and cimetidine are frequently prescribed in dosages excessive for elderly patients (Whiting, Wandless & Sumner 1978; Manning et al. 1980; Campion et al. 1985).

There is also the more insidious problem of drug side effects that go "undetected, untreated, and unexplained" by physicians (McKenney et al. 1973). These side effects often result from ingestion of many different kinds of medications concurrently and contribute to more serious adverse drug reactions. For example, one of the most common causes of reversible dementia is the injudicious use of medications (Kane, Ouslander & Abrass 1984; Beck et al. 1982).

Physicians' Perceptions of the Elderly. It is important to examine how physicians' perceptions of the elderly may influence drug misuse and its prevention. The results of one study showed that physician-patient encounter time declined as a function of age. This decline was observed for eight out of nine kinds of physicians studied, across the range of primary problem severity and regardless of the type of encounter (Kane et al. 1980; Keeler et al. 1982). The researchers suggested that physicians spend less time with the elderly, in part, because they do not consider aged persons to be priority patients. A lack of awareness of ways to observe and measure progress in elderly patients may aggravate negative attitudes, and inadequate time spent with these patients may affect the quality of physicians' diagnoses and prescribing.

Studies have also compared the attitudes of medical students toward the elderly at the start and end of their training. The studies show that, in general, there is deterioration in students' attitudes toward elderly patients and in their desire to care for them (Gale & Livesley 1974; Spence et al. 1968).

Misuse of Psychotropic Medications. As we noted earlier, a crucial drug misuse issue involves inappropriate prescribing of sedative-hypnotics. In a major study, the Institute of Medicine was unable to find documentation confirming the efficacy of hypnotics in the elderly (Institute of Medicine 1979). This is a shocking revelation in view of the disproportionately high use of sleeping pills by older persons and their much greater incidence of sleep-related respiratory impairment and cardiovascular disease. Since common hypnotic medications, such as chloral hydrate and flurazepam, are more likely to produce side effects in the aged, long-term regimens of sleeping pills should be seriously questioned.

The elderly are more likely to fall and sustain hip fractures if they use psychotropic drugs (such as antipsychotics, tricyclic antidepressants, and long-acting hypnotic or antianxiety agents). A study by Ray and his colleagues (1987) is the first to show a consistent association between the use of psychotropic drugs and hip fractures in both the institutionalized and noninstitutionalized aged. Researchers found that Michigan Medicaid enrollees over 65 who used an antipsychotic drug were twice as likely to fracture a hip as were nonusers, and that taking a tricyclic antidepressant increased the risk of hip injury by nearly 100 percent. Using hypnotic or antianxiety drugs that have long elimination half-lives (i.e., that take the body a day or more to eliminate) increased chances by 80 percent for breaking a hip. Higher dosages increased risk of hip fracture even more. Nearly 14 percent of the hip fractures in the population studied were attributable to falls produced by side effects of psychotropic drugs. If the study findings are confirmed in other populations, it means that a large percentage of all hip fractures among the elderly may be caused indirectly by the use of psychotropic drugs.

Undermedication. Overmedication is often seen as the major drug misuse problem plaguing the elderly, but undermedication may be an equally serious and frequently overlooked phenomenon. We have anectodal evidence to suggest that many chronic illnesses and syndromes afflicting the elderly--depression, arthritis, diabetes, osteoporosis, and the chronic pain syndrome often accompanying metastatic cancer--may be undertreated by physicians. Physicians may fail to prescribe needed drugs, or may prescribe them in less than adequate amounts for an insufficient period of time. In a major prospective randomized controlled trial examining the impact of clinical pharmacists' consultations on geriatric drug prescribing and use, preliminary findings suggest that a full 17 percent of patients were prescribed a dose that was too low to achieve therapeutic effect (Assessment of Prescribing Practices for a Geriatric Population, APHA Abstract, Lipton and Bero 1989).

Another area in which undermedication is apparent and potentially serious is in the treatment of depression. Physicians may fail to treat depression in elderly patients because it can exhibit atypical symptoms. Mental confusion, for example, may indicate depression. When it is correctly identified, it may not be treated at all because physicians may consider depression an inherent part of aging. Even when antidepressant drug therapy is initiated, dosages may be too low because physicians are either overly cautious or are unaware of the availability of antidepressant drugs with differing side-effect profiles. Such variety permits physicians to individualize therapy by monitoring blood levels (Task Force on Use of Laboratory Tests in Psychiatry 1985).

Another instance of undermedication can be observed in the use of chemotherapeutic agents for cancer. Geriatric patients often are omitted from chemotherapeutic treatment for fear that they will develop life-threatening toxicities. When they are placed on chemotherapeutic treatment, clinicians may assume that the dosages of these drugs should be reduced because of the potential for serious adverse drug reactions. In fact, recent evidence suggests that in order to produce any therapeutic effect in older adults, these agents must be given in full dosages (Kelly 1986).

Inappropriate physician prescribing for the elderly patient can result in rapid hospitalization. It is estimated that up to 10 percent of hospital admissions and readmissions may be caused by adverse drug reactions, often a result of inappropriate prescribing. Geriatric patients are especially at risk (Hurwitz 1969; Learoyd 1972; Wynne & Heller 1973; Williamson 1979). Not all drug-related hospitalizations are preventable. Some are unavoidable reactions produced by the prescribing of necessary drugs in appropriate dosages. However, hospitalizations that result from inappropriate dosages, avoidable drug-drug interactions, or physicians' lack of awareness of the increased toxicity of many drugs in the elderly are preventable.

Noncompliance. Another major area of medication misuse among the elderly living in the community is noncompliance with drug therapy. Patient noncompliance can take many forms: underuse, overuse, or inappropriate use of drug therapies. It can be intentional or unintentional. Whatever its form or intent, one thing is clear: noncompliance is widespread among ambulatory elderly, estimated conservatively at about 40%. The elderly are particularly vulnerable to noncompliance because many of the risk factors are characteristic of the elderly population (Table 3). Each of these risk factors will now be discussed.

Multiple Drug Regimen

A consistent finding in studies of drug use is that there is an inverse relationship between patient compliance and the number of drugs taken by the patient (Malahay 1966; Francis, Korsch & Morris 1969; Latiolas & Berry 1969; Weintraub, Au & Lasagna 1973; Hulka et al. 1975; Parkin et al. 1976; Caplan et al. 1976; Darnell et al. 1986). Because 25 percent of elderly persons consume three or more drugs as part of their daily treatment plan (compared to 9 percent of younger persons), the elderly are particularly at risk for noncompliance (American Association of Retired Persons 1984).

Duration of Drug Treatment

Compliance decreases with time. The percentage of patients who carefully adhere to treatment plans for hypertension and other chronic diseases--diseases to which the elderly are particulary susceptible--rapidly declines after the initial diagnosis and early months of treatment (Rudd et al. 1979; Haynes et al. 1982). Patients who are fully compliant during their hospitalization may become noncompliant when going back into the community (Hare & Willcox 1967; Irwin, Weitzell & Morgan 1971). The explanation for these findings might be that patients' drug therapy is closely supervised in the hospital and at initial diagnosis, but is not monitored as carefully when discharged to the community.

Health Status

The health status of the elderly makes them exceptionally vulnerable to noncompliance. Almost half of the noninstitutionalized elderly are limited in mobility because of chronic conditions (Kovar 1977; Rice & Estes 1984). Decreased activity and dexterity can limit a person's ability and willingness to have prescriptions filled, take drugs regularly, and open and close the childproof containers that, to arthritic hands, are unmanageable.

Vision and hearing impairments, which afflict many of the elderly, contribute to noncompliance, too. Failing eyesight reduces the ability to read small print on prescription labels and package inserts (Dirckx 1979). About 30 percent of the population aged 65 and older suffer significant hearing loss (Butler & Lewis 1977; National Center for Health Statistics 1985) which limits patients' ability to hear directions for appropriate drug use and discourages them from asking questions for fear they might not hear the answers (Ebersole & Hess 1981). Hearing loss also contributes to social isolation--another factor characteristic of noncompliance.

For some elderly patients, memory loss is also a critical problem. Sometimes the problem is related to prescribed medications; other times, it is the far more serious senile dementia. Because, in its early stages, senile dementia may be difficult to recognize, physicians and others involved with a patient may not foresee possibilities for noncompliance.

Social Isolation

Compliance tends to be a greater problem when patients are socially isolated (Haynes, Sackett & Taylor 1980; Hussar 1975; Blackwell 1973; Porter 1969), although we do not know why. One study reported that potentially serious medication errors were made by 42 percent of patients living alone, whereas such errors were made by 18 percent of those living with one or more persons (Schwartz et al. 1962). Social isolation is more common among the elderly living in the community, particularly among elderly women, than among any other age group. One quarter of the nation's elderly live alone, and the numbers are growing.

Knowledge of the Drug Regimen

A number of studies have observed that when a patient is provided with specific and detailed instruction about his or her particular drug regimen, compliance improves (Svarstad 1976; Hulka et al. 1976; Svarstad 1986). It has also been documented that elderly people lack basic information about their drugs. They are uninformed about the name and purpose of their drugs, the dosage schedules, the duration of the regimen and its possible side effects or adverse consequences (Schwartz et al. 1962; Cooper 1978; Lundin et al. 1980; Lofholm 1978; Klein et al. 1982). While mastery of this basic information does not ensure compliance, ignorance can certainly predispose patients to noncompliance.

Physicians' drug instructions are often given hastily at the end of the patient's visit and are usually fragmentary, incomplete, and general (Svarstad 1976, 1986). Basic information, such as the purpose of the drug, expected treatment outcomes, duration of drug regimen, and dosage schedule and frequency is frequently not provided (Hulka et al. 1976; Svarstad 1976; Francis, Korsch & Morris 1969). Sometimes patients receive no instruction at all; the physician assumes that the patient has already been given instructions by other health professionals.

Patient Deference Toward Health Professionals

Older patients are often reticent and do not ask questions or express concerns to physicians or pharmacists (DeSimone, Peterson & Carlstedt 1977; Miller 1983). Their respect for professional authority makes them reluctant to challenge it. Other patients are afraid of looking unintelligent or unsophisticated. Still others are simply too sick or too anxious to ask questions.

For their part, physicians rarely invite questions from patients regarding proposed drug therapy. When physicians do talk about a patient's regimen, they often do so in ways that brook no opposition--for example, "You are taking all of your medications, aren't you?" Physicians may also answer questions relating to drug therapy with one- or two-word responses. Thus, patterned deference of patients toward doctors--the conspiracy of silence--is maintained. Under these conditions, misconceptions remain uncorrected, and worries, unassuaged, and chances for noncompliance are increased. The ultimate victim, of course, is the patient, whose therapeutic outcome is compromised.

Drug Costs

Yet another barrier to safe and effective drug use is economic: patients' inability to afford prescription drugs in the amounts called for by prescription directions. Elderly who are on minimal, fixed incomes may be unable to purchase necessary drugs, forcing them to discontinue critical drug therapy (Smith 1979; Lamy 1980; Simonson 1984). These concerns have been corroborated by elderly patients' personal accounts provided in Congressional hearings as well as by research studies. For example, in a study of 290 chronically ill patients discharged from a general hospital in Canada, researchers found that the financial burden imposed by drug costs was the primary reason given by patients for noncompliance with drug treatment. Other studies have corroborated that drug costs may be a factor in noncompliance with physicians' instructions (Brand, Smith & Brand 1977).

Overall, the elderly pay 14% more per prescription than the nonelderly. It is important to note that the elderly are not being charged more for their medications; rather, they take a different mix of drugs, and the size of their prescriptions is larger because they are on long-term drug therapy. As noted previously, there has been an increase in the number of prescriptions per capita for the elderly, from 10.5 prescriptions in 1967 to an estimated 18 prescriptions in 1988 (Waldo 1987).

Because they use increasingly more prescriptions and pay higher prices for prescriptions than do younger patients, the elderly are more likely to incur large drug costs. They are also more likely to pay a higher percentage of their drug expenses out-of-pocket. Although the aged spend more on drugs than any other age group, the share of their drug expenses paid by private insurance is less than for the population as a whole.

What about the distribution of drug costs within the elderly population, broken down by economic status? Results of a 1980 national survey (NMCUES) revealed that while the proportion of prescription drug expenses reimbursed by private insurance was similar among poor and near-poor elderly (7.7 percent and 10.7 percent, respectively), it was significantly higher--in fact, double--among those who were not poor (20.6 percent). Note that all three groups, including those living at or below the poverty level, had to pay over half their drug expenses out-of-pocket (Table 4).

It is important to emphasize that this information was collected in 1980, before the escalation of drug prices. Drug prices have increased two to three times faster than all consumer prices since 1981, while the real income for the aged poor and near-poor has remained relatively static in recent years. Social Security payments have increased at about the same rate as general inflation, but drug price inflation has far exceeded general inflation--making the burden of drug expenditures even heavier on the elderly dependent on Social Security.

Because many elderly patients pay significant out-of-pocket costs for drugs and because prescription drug prices have increased two to three times faster than all consumer prices since 1981, drug prices have become a source of growing concern for consumers, policymakers, and individual and institutional purchasers. In recent years trends in drug prices have been changing. Before 1981, prescription drug prices rose more slowly than did the Consumer Price Index. Beginning in 1981, however, prescription drug prices started rising faster than the CPI (Table 5). In 1988, for example, when the overall inflation rate was 4.1 percent, the drug price inflation rate was 7.9 percent. Thus, for the most recent year for which data were available, drug price increases grew almost two times faster than the CPI.

Particularly burdened by these escalating drug prices are those elderly living in the community with fixed incomes, high drug costs, and inadequate or no prescription drug coverage.

Strategies to Treat Noncompliance

It is important to note that strategies to prevent, detect, and treat noncompliance are known and have been used successfully in geriatric populations in community settings (Lipton and Lee 1988). These strategies are summarized in Tables 6, 7, and 8.

Consequences of Noncompliance

Noncompliance can have enormous clinical and economic consequences. Some clinical examples will illustrate this point:

- A 65-year-old patient with hypertension discontinues her medication because its side effects make her feel worse than she does when she is not on medication. Her high blood pressure is no longer controlled, and she eventually has a stroke leading to prolonged hospitalization and permanent disability.
- An 80-year-old man suffering from depression stops taking his antidepressants because he sees no improvement in his condition after one week of drug therapy. His depression worsens and he is eventually hospitalized. What he did not know was that the benefits of some antidepressants become apparent only after the drugs have been taken for several weeks.
- A 75-year old patient on diuretic therapy and digoxin for congestive heart failure stops taking his potassium supplement because he finds it unpalatable. It seems to him that his condition is under control without the supplement. Eventually, he becomes hypokalemic--low in potassium.

The potassium deficiency, in combination with digoxin, creates heart rhythm disturbances in the patient, which leads to an emergency room visit and subsequent hospitalization.

Some researchers suggest that about 10 percent of hospital admissions result from poor patient compliance and that geriatric patients are particularly at risk (Graham & Livesley 1983; Frisk, Cooper & Campbell 1977). Noncompliance, of course, is not the only cause of drug-related hospitalizations. As we have already mentioned, adverse drug reactions--often resulting from inappropriate physician prescribing--are also implicated. There is evidence to suggest that patient noncompliance and adverse drug reactions taken together account for about 15 percent of geriatric hospitalizations (McKenney & Harrison 1976; Bergman & Wiholm 1981; Graham & Livesley 1983; Frisk, Cooper & Campbell 1977; Williamson 1979; Caranasos, Stewart & Cluff 1974). But it is important to stress that these studies are not very rigorous and there is enormous variability in these estimates. More research is clearly needed in this important area.

IV. Prescriptions for Change

In previous sections we have analyzed patterns of drug use and misuse among elderly patients living in the community. In this section we propose specific actions that should be taken now to help improve the quality and economy of drug prescribing for our elderly's noninstitutionalized population.

Expanded Research Agenda

Needed are large-scale, epidemiologic studies examining the relationship between patterns of drug use and misuse and clinical outcomes.

We have already discussed one such study linking psychotropic drug use and hip fractures (Ray et al. 1987). Considering that hip fracture is a leading cause of morbidity and mortality among the elderly, occurring in nearly a quarter of a million patients--for a total cost of almost $6 billion a year--this is important, policy-relevant research. Other studies like it should be encouraged.

We also need to know much more about the consequences of inappropriate geriatric drug prescribing and use among the elderly. A critically important question is: What kinds of specific drug therapy problems lead to adverse outcomes like drug-induced hospitalizations? Given the current, well-deserved, emphasis on rigorous assessment of health care outcomes, it is extremely important to develop a systematic tool to assess the incidence and characteristics of drug-related hospital admissions in geriatric populations, and to determine which of these are preventable. Professional Review Organizations may be able to incorporate such an assessment tool into their review of medical records.

Federally sponsored studies should be conducted to give us information on the costs of expanded drug coverage under the Medicare Catastrophic Coverage Act, and the distribution of such costs by beneficiaries' age, gender, income, health status, and health insurance coverage. Policymakers could then use the information to adjust the amounts of deductibles, coinsurance, and premiums. If the costs incurred by the program were either greater or less than projected, the deductible, coinsurance, and premium levels could be altered accordingly. Such information would allow Medicare to direct services to groups most needing them, that is, people with low incomes, high drug costs, and no or limited drug coverage. The drug benefit could then be changed to permit a fairer and more equitable distribution of resources among the elderly living in the community.

Improving Medical Education

Most medical schools have not developed even minimal programs related to geriatrics in general and drugs and the elderly in particular.

Many health professionals do not like working with elderly patients. Physicians, in particular, have been inculcated early in their training with the belief that "cure" of pathology is the goal of treatment. However, most conditions afflicting the elderly are chronic. By definition, they cannot be "cured." Health professionals must learn that fostering functional independence--enhancing patients' abilities to carry out activities of daily living--is a valuable treatment goal in itself.

Negative attitudes toward the elderly involve more than the inability to cure the aged of chronic disease; they also mirror larger societal stereotypes about aging. Physicians need to be educated about attitudes toward age and about the possible harmful effects of negative attitudes on quality of care, including the quality of physician prescribing. An important aspect of education is information on the specific abilities and potential of the elderly. A foundation can be laid if comprehensive geriatric programs are integrated into medical schools' curricula. Curricular changes should include emphasis on the principles of geriatric pharmacotherapy and the previously enumerated strategies that physicians can use to prevent, detect, and treat noncompliance by elderly patients.

Role of the Clinical Pharmacist

Today's highly trained clinical pharmacists can do much more than "count and pour and lick and stick." They are capable of monitoring drug-drug interactions (including interactions between prescription and nonprescription drugs), inappropriate dosage and duration of drug therapies, contraindicated drugs, and inappropriate choice of drug therapies. Clinical pharmacists can enhance physicians' drug therapy decisions, improve patient compliance, curtail drug costs, and reduce outpatient visits and hospitalizations (Bond & Salinger 1979; Sczupak & Conrad 1977; Hood & Murphy 1978). These outcomes have been demonstrated in teaching hospitals (Keys, South & Duffy 1975; Brooks et al. 1977; Herfindal, Bernstein & Kishi 1983), in outpatient settings (McKenney et al. 1973; McKenney et al. 1978; Rosen & Holmes 1978), in home-based populations (Hammarlund et al. 1985), and in skilled nursing facilities (Cheung & Kayne 1975; Strandberg et al. 1980, Kidder 1987). But in order to make these judgments, clinical data--particularly diagnostic information and a complete record of the patient's drug regimen--are essential. The proposed electronic claims processing data base being developed for use by pharmacists participating in the Medicare Catastrophic Coverage Act need to contain more than utilization and eligibility information in order to make maximum use of the community pharmacists' skills in serving the noninstitutionalized elderly.

Clinical pharmacists in hospitals can also play a critical role in community-based care. Because they have access to physicians, to patients, and to pertinent clinical and diagnostic data, these pharmacists can identify elderly patients at risk for drug misuse (e.g., those patients who, when discharged, are taking three or more chronic medications). Such patients can then be provided with intensive medication counseling before discharge and at periodic intervals during the critical postdischarge period when drug-related problems are most likely to emerge. During these consultations, pharmacists can identify drug problems (e.g., dose scheduling and administration difficulties) that may compromise therapy, and then provide appropriate solutions. Pharmacists can also alert patients' physicians to potentially serious drug therapy problems (e.g., drug-drug interactions). This model of care--hospital-based pharmacists serving as drug therapy consultants for hospitalized and outpatient geriatric patients and their physicians--is currently being evaluated at the El Camino Hospital in Mountain View, California, with funding provided by the John A. Hartford Foundation in New York City.

Should this innovative model prove successful, it should be implemented and evaluated in other settings in which large numbers of elderly patients receive care (e.g., Veterans' Administration hospitals) with funding from the Health Care Financing Administration.

Finally, the Medicare program should fund large-scale demonstration projects to evaluate the effectiveness of using clinical pharmacists as drug consultants to community-based physicians directly in their offices. Such "public-interest detailing" has proved to be successful in randomized controlled trials performed in several states (Avorn and Soumerai 1983). These kinds of activities could be performed on a regional basis by pharmacy schools under contract with HCFA. If public-interest detailing proves effective on a national scale, it could be integrated into the Medicare program.

If these proposed recommendations are implemented, they have the potential not only to make drugs affordable to a population for whom they are life-saving/life-enhancing technologies but also to improve quality of care and to effect cost savings for elderly patients living in the community.

Our nation's elders--and our society--deserve no less.

Table 1

Drug mention rate per 1,000 visits for the 10 drugs most frequently ordered or provided to patients 65 and over, United States, 1980

Drug	Drug Mention Rate Per 1,000 Visits	Drug	Drug Mention Rate Per 1,000 Visits
Female Patients 65 years or older		Male Patients 65 years or older	
Lanoxin (digoxin)	50.8	Lasix (furosemide)	56.6
Lasix (furosemide)	48.2	Lanoxin (digoxin)	52.3
Dyazide (triamterene)	43.0	Inderal (propranolol)	40.5
Inderal (propranolol)	42.4	Digoxin	38.1
Aldomet (methyldopa)	34.0	Isordil (isosorbide)	28.8
Vitamin B-12	32.7	Dyazide (triamterene)	24.1
Digoxin	29.5	Aspirin	19.3
Motrin (ibuprofen)	24.1	Hydrochlorothiazide	19.2
Insulin	22.7	Hydrodiuril (hydrochlorothiazide)	18.7
Hydrochlorothiazide	22.0	Prednisone	18.0

Source: National Center for Health Statistics & Bloom (1982): 7

NOTE: "Drug mention rate" is the average number of drugs ordered or provided per office visit.

Table 2

Drug Groups Ranked by Frequency of Use in Age Groups

	Age Group			
Drug Groups	45-54	55-64	65-74	75+
Systemic antiarthritics	1	2	1	2
Beta-blockers	2	1	2	6
Thiazide and related diuretics	3	3	3	4
Digitalis preparations	34	9	4	1
Potassium-sparing diuretics	5	4	5	5
Other oral diuretics (e.g., furosemide)	18	8	6	3
Other antihypertensives (e.g., methyldopa)	8	5	8	8
Nitrate/nitrite coronary vasodilators	16	7	7	7
Benzodiazepine tranquilizers	4	6	10	12
Oral diabetes therapy	17	11	9	9

Source: National Disease and Therapeutic Index, IMS America, Ltd., 1982 (as cited in Baum, Kennedy & Forbes 1985: 65).

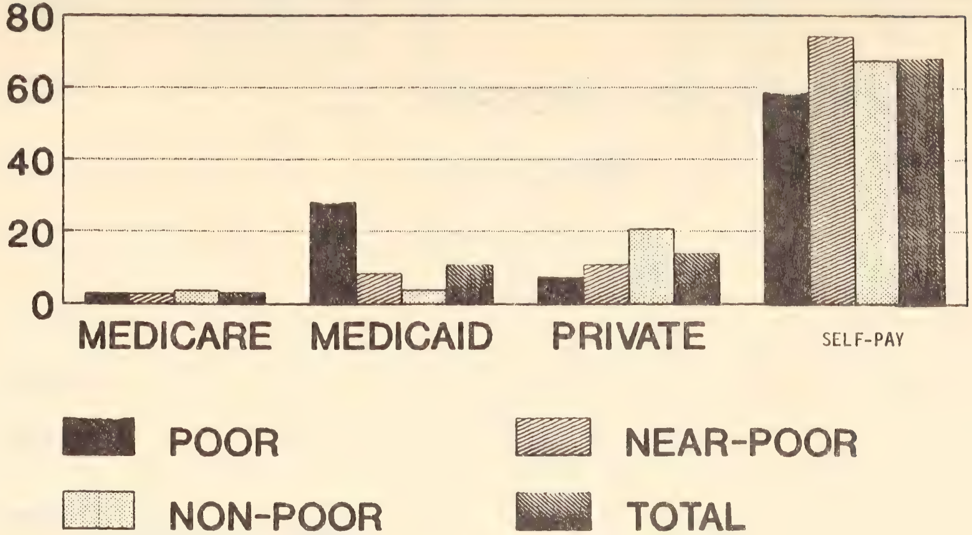
Table 3

FACTORS ASSOCIATED WITH NONCOMPLIANCE AMONG GERIATRIC PATIENTS

- MULTIPLE DRUG REGIMEN
- DURATION OF DRUG TREATMENT
- HEALTH STATUS
- SOCIAL ISOLATION
- KNOWLEDGE OF THE DRUG REGIMEN
- PATIENT DEFERENCE TOWARD HEALTH PROFESSIONALS
- DRUG COSTS

Table 4

PAYMENT DISTRIBUTION FOR RX DRUGS USED BY MEDICARE BENEFICIARIES, 1980



NATIONAL MEDICAL CARE UTILIZATION AND EXPENDITURE SURVEY

Table 5

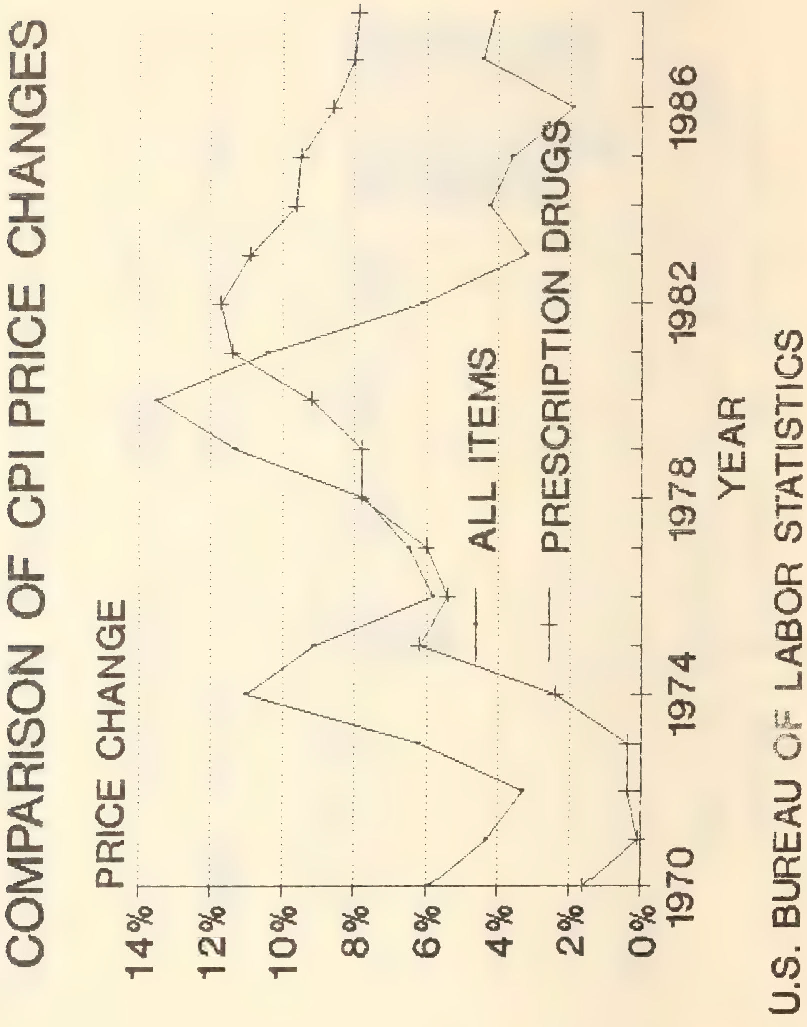


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Table 6

Strategies to Prevent and Treat Noncompliance among the Elderly:

The Drug Regimen

Barrier to Compliance: Characteristics of the Drugs or Regimen	Strategy
Multiple drug regimen	Put name and purpose of medication on containers Label in a simple, direct, and understandable manner (e.g., "digoxin--heart pill") Simplify scheduling of medications by titrating medications against treatment response to determine the least amount of medication required, and by eliminating unnecessary medications Use a patient profile system
Long duration of regimen	Monitor for continued compliance Periodically assess patient status and review drug regimen with patient
Types of Drug Prescribed	Put names and purposes of medication on containers Label in a simple, direct, and understandable manner

Source: Lipton & Lee, 1988

Table 7

Strategies to Prevent and Treat Noncompliance among the Elderly:

Dealing with the Patient's Physical and Mental Impairments

Barriers to Compliance: Physical and Mental Impairments	Strategy
Hearing impairment that cannot be corrected with appropriate intervention	Speak loudly and slowly Face the patient directly
Vision impairment that cannot further corrected	Label all written information with large be letters using boldface type Use a color-coding system
Memory loss	Distribute patient package inserts to reinforce physician, pharmacist, and nurse instructions and to serve as home reference guides[a] Repeat instructions Evaluate patient's comprehension of drug instructions, using nonthreatening, nonjudgmental questions Use electronic bottlecap for pills (e.g., Med-Tymer)
Dexterity problems	Advise of the availability of nonchildproof medication containers

(a) Patient package inserts (PPIs) may be especially helpful to older patients. A large study of PPIs found that older patients read them more often, resulting in a small but detectable increase in patient knowledge about medications (Kanouse et al. 1981).

Source: Lipton & Lee, 1988

Table 8

Strategies to Prevent and Treat Noncompliance among the Elderly:

Social, Cognitive, Behavioral, and Economic Problems

Barriers to Compliance: Social, Cognitive, Behavioral, and Economic Problems	Strategy
Social isolation	Distribute medication calendars Use electronic bottlecap for pills Involve available family members, friends and others in the patient's social support network (Haynes 1976; Shaw & Opit 1976)
Lack of knowledge about drug use	Provide specific and detailed oral and written information about the drug regimen, including purpose and type of medication prescribed, brand or generic name, dosage schedule, duration of therapy, and information on whether the drug should be taken continuously or symptomatically (Svarstad 1976; Hulka et al. 1976; McKenney et al. 1973; McKenney et al. 1978).
Deference toward health professionals	Provide older patients time to ask questions Introduce a contingency contract
Cost of drugs	Substitute generic drugs or less costly alternatives Suggest nondrug alternatives Discourage the use of unnecessary nonprescription drugs

Source: Lipton & Lee, 1988

References

American Association of Colleges of Pharmacy and Eli Lilly and Company. 1985. Pharmacy practice for the geriatric patient. Carrboro, N.C.: Health Sciences Consortium.

Avorn, J., and S. B. Soumerai. 1983. Improving drug-therapy decisions through educational outreach: A randomized controlled trial of academically based "detailing." New England Journal of Medicine 308: 1457-63.

Beck, J. C., et al. 1982. Dementia in the elderly: The silent epidemic. Annals of Internal Medicine 97: 231-41.

Bergman, U., and B. E. Wiholm. 1981. Drug-related problems causing admission to a medical clinic. European Journal of Clinical Pharmacology 20: 193-200.

Blackwell, B. 1973. Drug therapy: Patient compliance. New England Journal of Medicine 289: 249-52.

Bond, C. A., and R. J. Salinger. 1979. Fluphenazine outpatient clinics: a pharmacist's role. Journal of Clinical Psychology 1: 501-503.

Brand, F. N., R. T. Smith, and P. A. Brand. 1977. Effect of economic barriers to medical care on patients' noncompliance. Public Health Reports 92: 72-78.

Brooks, P. M., et al. 1977. Reducing the pill swill: An audit of clinical pharmacy. Medical Journal of Australia 2: 427-28.

Butler, R. N., and M. I. Lewis. 1977. Aging and mental health. St. Louis, Mo.: C. V. Mosby.

Campion, E. W., et al. 1985. Age, weight, and dose in drug prescribing for ambulatory elders. Paper presented at the Gerontological Society of America Meeting, San Antonio, Texas, Nov. 22-26, 1985 (abstract).

Caplan, R. D., et al. 1976. Adhering to medical regimens: Pilot experiments in patient education and social support. Ann Arbor, Mich.: The Institute for Social Research of the University of Michigan.

Caranasos, G. J., R. B. Stewart, and L. E. Cluff. 1974. Drug-induced illness leading to hospitalization. Journal of the American Medical Association 288: 713-17.

Cheung, A., and R. Kayne. 1975. An application of clinical pharmacy services in extended care facilities. California Pharmacist 23: 22-28.

Cooper, J. W. 1978. Drug therapy in the elderly: Is it all it could be? American Pharmacy NS18: 25-26.

Darnell, J. C., et al. 1986. Medication use by ambulatory elderly: An in-home survey. Journal of the American Geriatrics Society 34: 1-4.

DeSimone, E. M., C. F. Peterson, and B. C. Carlstedt. 1977. Pharmacist-patient interaction and patient expectations. American Journal of Pharmaceutical Education 416: 167-71.

Dirckx, J. H. 1979. Labels for prescribed drugs. Letter. Journal of the American Medical Association 242: 413-14.

Ebersole, P., and P. Hess. 1981. Toward healthy aging: Human needs and nursing response. St. Louis, Mo.: C. V. Mosby.

Francis, V., B. M. Korsch, and M. J. Morris. 1969. Gaps in doctor-patient communication: Patients' response to medical advice. New England Journal of Medicine 280: 535-40.

Frisk, P. A., J. W. Cooper, and N. A. Campbell. 1977. Community-hospital pharmacist detection of drug-related problems upon patient admission to small hospitals. American Journal of Hospital Pharmacy 34: 738-42.

Gale, J., and B. Livesley. 1974. Attitudes towards geriatrics. Age and Ageing 3: 49-53.

Graham, H., and B. Livesley. 1983. Can readmissions to a geriatric medical unit be prevented? Lancet 1: 404-6.

Grymonpre, R. E., et al. 1988. Drug-associated hospital admissions in older medical patients. Journal of the American Geriatrics Society. 36: 1092-98.

Hammarlund, E. R., J. R. Ostrom, and A. J. Kethley. 1985. The effects of drug counseling and other educational strategies on drug utilization of the elderly. Medical Care 23: 165-70.

Hare, E. H., and D. R. Willcox. 1967. Do psychiatric inpatients take their pills? British Journal of Psychiatry 113: 1435-39.

Haynes, R. B., D. L. Sackett, and D. W. Taylor. 1980. How to detect and manage low patient compliance in chronic illness. Geriatrics 355: 91-97.

Haynes, R. B., et al. 1982. Process versus outcome in hypertension: A positive result. Circulation 65: 28-33.

Herfindal, E. T., L. R. Bernstein, and D. T. Kishi. 1983. Effect of clinical pharmacy services in prescribing on an orthopedic unit. American Journal of Hospital Pharmacy 40: 1945-51.

Hood, J. C., and J. E. Murphy. 1978. Patient noncompliance can lead to hospital readmissions. Pharmacy 52: 79-82, 84.

Hulka, B. S., et al. 1975. Medication use and misuse: Physician-patient discrepancies. Journal of Chronic Diseases 28: 7-21.

Hulka, B. S., et al. 1976. Communication, compliance, and concordance between physicians and patients with prescribed medications. American Journal of Public Health 66: 847-53.

Hurwitz, N. 1969. Predisposing factors to adverse drug reactions. British Medical Journal 1: 536-39.

Hussar, D. A. 1975. Patient noncompliance. Journal of the American Pharmaceutical Association 15: 183-90, 201.

Institute of Medicine. 1979. Sleeping pills, insomnia, and medical practice. Washington, D.C.: National Academy of Sciences.

Irwin, D. S., W. D. Weitzell, and D. W. Morgan. 1971. Phenothiazine intake and staff attitudes. American Journal of Psychiatry 127: 1631-35.

Ives, T. J., E. J. Bentz, and R. E. Gwyther. 1987. Drug-related admissions to a family medicine inpatient service. Archives of Internal Medicine 147: 1117-29,

Kane, R. L., J. G. Ouslander, and I. B. Abrass, eds. 1984. Essentials of clinical geriatrics. New York: McGraw-Hill.

Kane, R. L., et al. 1980. Geriatrics in the United States: Manpower projections and training considerations. Santa Monica, Calif: Rand Corporation.

Keeler, E. B., et al. 1982. Effect of patient age in duration of medical encounters with physicians. Medical Care 20: 1101-8.

Kelly, J. F. 1986. Clinical pharmacology of chemotherapeutic agents in old age. In Cancer and the elderly, frontiers of radiation therapy and oncology, eds. J. M. Vaeth and J. Meyer, Vol. 20, pp. 101-11. Basel: S. Karger.

Keys, P. W., J. C. South, and M. G. Duffy. 1975. Quality of care evaluation applied to assessment of clinical pharmacy services. American Journal of Hospital Pharmacy 32: 897-902.

Kidder, S. W. 1987. Cost-benefit of pharmacist-conducted drug-regimen reviews. The Consultant Pharmacist September/October: 394-98.

Klein, L. E., et al. 1982. Aging and its relationship to health knowledge and medication compliance. Gerontologist 22: 384-87.

Kovar, M. G. 1977. Health United States, 1976-1977. DHEW Pub. No. (HRA) 77-1232, U.S. Department of Health, Education, and Welfare. Washington, D.C.: Government Printing Office.

Kusserow, R. P. 1989. Medicare drug utilization review. Office of Inspector General, Office of Analysis and Inspections, Department of Health and Human Services. Washington, D.C.

Lamy, P. P. 1980. Prescribing for the elderly. Littleton, Mass.: PSG Publishing.

Latiolais, C. and C. Berry. 1969. Misuse of prescription medication by outpatients. Drug Intelligence and Clinical Pharmacy 3: 270-77.

LaVange, L., and H. Silverman. 1987. Outpatient prescription drug utilization and expenditure patterns of noninstitutionalized aged Medicare beneficiaries. National medical care utilization and expenditure survey, Series B, Descriptive Report No. 12. DHHS Pub. No. 85-20212. Office of Research and Demonstrations, Health Care Financing Administration. Washington, D.C.: Government Printing Office.

Learoyd, B. M. 1972. Psychotropic drugs and the elderly patient. Medical Journal of Australia 22: 1131-33.

Lipton, H. L., and L. Bero. 1989. Assessment of prescribing practices for a geriatric population. American Public Health Association abstract submitted for APHA Annual Meeting, November 1989.

Lipton, H. L., and P. R. Lee. 1988. Drugs and the elderly: Clinical, Social, and Policy Perspectives. Stanford, CA: Stanford University Press.

Lofholm, P. 1978. Self-medication by the elderly. In Drugs and the elderly, ed. R. C. Kayne, pp. 8-28. Los Angeles: University of Southern California Press.

Lundin, D. V., et al. 1980. Education of independent elderly in the responsible use of prescription medications. Drug Intelligence and Clinical Pharmacy 14: 335-42.

Malahay, B. 1966. The effect of instruction and labeling on the number of medication errors made by patients at home. American Journal of Hospital Pharmacy 23: 283-92.

Manning, P., et al. 1980. Determining educational needs in the physician's office. Journal of the American Medical Association 244: 1112-15.

McKenney, J., and W. L. Harrison. 1976. Drug-related hospital admissions. American Journal of Hospital Pharmacy 33: 792-95.

McKenney, J. M., et al. 1973. The effect of clinical pharmacy services on patients with essential hypertension. Circulation 48: 1104-11.

McKenney, J. M., et al. 1978. Effect of pharmacist drug monitoring and patient education on hypertensive patients. Contemporary Pharmacy Practice 1: 50-56.

Miller, R. W. 1983. Doctors, patients don't communicate. FDA Consumer 17, July/Aug. 1983, pp. 6-7.

National Center for Health Statistics. 1985. Current estimates from the National Health Interview Survey: United States, 1982. Vital and Health Statistics Series 10, No. 150, DHHS Pub. No. (PHS) 85-1578. Washington, D.C.: Government Printing Office, Sept. 1985.

Parkin, D., et al. 1976. Deviation from prescribed drug treatment after discharge from hospital. British Medical Journal 2: 686-88.

Popplewell, P. Y., and P. J. Henschke. 1982. Acute admissions to a geriatric assessment unit. Medical Journal of Australia April: 343-4.

Porter, A. M. W. 1969. Drug defaulting in a general practice. British Medical Journal 1: 218-22.

Ray, W. A., et al. 1987. Psychotropic drug use and the risk of hip fracture. New England Journal of Medicine 316: 363-69.

Rice, D. P., and C. L. Estes. 1984. Health of the elderly: Policy issues and challenges. Health Affairs 3: 25-49.

Rosen, C. E., and S. Holmes. 1978. Pharmacists' impact on chronic psychiatric outpatients in community mental health. American Journal of Hospital Pharmacy 35: 704-8.

Rudd, P., et al. 1979. Hypertension continuation adherence. Archives of Internal Medicine 139: 545-49.

Schwartz, D., et al. 1962. Medication errors made by the elderly, chronically ill patients. American Journal of Public Health 52: 2018-29.

Sczupak, C. A., and W. F. Conrad. 1977. Relationship between patient-oriented pharmaceutical services and therapeutic outcomes of ambulatory patients with diabetes mellitus. American Journal of Hospital Pharmacy 34: 1238-42.

Simonson, W. 1984. Medications and the elderly: A guide for promoting proper use. Rockville, Md.: Aspen Systems.

Smith, C. R. 1979. Use of drugs in the aged. Johns Hopkins Medical Journal 145: 61-64.

Spence, D. L., et al. 1968. Medical student attitudes toward the geriatric patient. Journal of the American Geriatrics Society 16: 976-83.

Strandberg, L. R., et al. 1980. Effect of comprehensive pharmaceutical services on drug use in long-term care facilities. American Journal of Hospital Pharmacy 37: 92-94.

Svarstad, B. L. 1976. Physician-patient communication and patient conformity with medical advice. In The growth of bureaucratic medicine: An inquiry into the dynamics of patient behavior and the organization of medical care, ed. D. Mechanic, pp. 220-38. New York: Wiley.

-----. 1986. Patient-practitioner relationships and compliance with prescribed medical regimens. In Application of social science to clinical medicine and health policy, eds. L. Aiken and D. Mechanic, pp. 438-59. New Brunswick, N.J.: Rutgers University Press.

Task Force on Use of Laboratory Tests in Psychiatry. 1985. Tricyclic antidepressants--Blood level measurements and clinical outcome: An APA task force report. American Journal of Psychiatry 142: 155-62.

Waldo, D. R. 1987. Outpatient prescription drug spending by the Medicare population. Health Care Financing Review 8, Fall 1987, forthcoming.

Weintraub, M., W. Au, and L. Lasagna. 1973. Compliance as a determinant of serum digoxin concentration. Journal of the American Medical Association 224: 481-85.

Whiting, B., I. Wandless, and D. J. Sumner. 1978. A computer-assisted review of digoxin therapy in the elderly. British Heart Journal 40: 8-13.

Williamson, J. 1979. Adverse reactions to prescribed drugs in the elderly. In Drugs and the elderly, eds. J. Crooks and I. H. Stevenson, pp. 239-46. Baltimore, Md.: University Park Press.

Williamson, J., and J. M. Chopin. 1980. Adverse reactions to prescribed drugs in the elderly: A multicentre investigation. Age and Ageing 9: 73-80.

Wynne, R. D., and F. Heller. 1973. Drug overuse among the elderly: A growing problem. Perspectives on Aging 11: 15-18.

Mr. DOWNEY. Dr. Gilmour, it's good to have you. I understand you also got up early this morning.

STATEMENT OF MONROE T. GILMOUR

Dr. GILMOUR. Thank you very much, Mr. Chairman.

My name, as you have noted, is Dr. Monroe Gilmour. I serve on AARP's Board of Directors. AARP is pleased to discuss with you these problems, because medication misuse creates, among older adults, serious difficulties. We believe this is a critical issue and one in which you can have a helpful effect. So we commend your committee for holding these timely hearings.

The problems resulting from misuse of medication have been clearly documented, and indeed, there is some reason to believe that the statistics actually underestimate the problem. As the recent HHS Inspector General's report indicated, in 1985, over a quarter of a million older adults were hospitalized for adverse drug reactions. Thousands more suffer mental impairment or risk misdiagnosis as a result of their reaction to medications and may, indeed, be at risk also for addiction to tranquilizers or sleeping pills. Thus, it is properly dubbed, as you have already noted, "America's other drug problem". Its cost in human terms and in dollars is incalculable, but the latter has been estimated to be as much as $7 billion a year.

As a family internist who dealt with patients for 46 years, I can testify to the urgent importance of this medication issue. Any medicine can react differently in any patient. Any patient, no matter how well instructed, may forget to take his medication, or forget he has taken it and take another dose. Very few medicines are taken exactly as prescribed at any age. Various medicines may react adversely with each other, or with certain food and drink, and the cost may keep a person from taking a medicine or from taking enough to reach a therapeutic level.

There are many reasons for these problems, as you already well know. That is why you're here. You can influence some of these reasons. Among these is the fact that much of the testing of medication has been done in the past in younger people, and thus, test results often did not take into account the physiological changes that occur with aging, which also has an effect on the medication results. Dr. Young and his group have already testified that this is improving.

Further, medical and other provider education is still scant and inadequate in the geriatric field, though that, too, is improving, but not enough. I would add one word. It needs to be improved in medical schools, but it's going to be 6 or 8 years before they come on line. It needs to be improved in graduate schools. And where it really needs to be improved is among the physicians already in the field practicing. You can encourage education and enhance it for doctors already in the field. Dr. Egelberg and others have already thought about that and I hope you can follow through on it.

The failure of patients to receive or to understand instructions and warnings about the benefits and hazards of their medicine is another reason for concern. Crowded labels, too small labels, confusing instructions, only compound the difficulty. Even the package inserts which AARP advocates, unless written clearly, simply and understandably, as Dr. Young indicated they wanted done, may frighten the patient into not taking the medicine or into taking less than prescribed. Patients do not ask enough questions of their doctors, and doctors don't foresee the questions that should have been asked and don't answer enough questions that are not asked.

We at AARP hope that the implementation of a drug utilization review system as part of the Medicare prescription drug provision will eventually have an impact on preventing medication interactions and reactions, as well as on inappropriate dosages. We strongly advocate that Congress use its powers to ensure that quality is not sacrificed on the "alters" of cost containment. Better management of medication would, in itself, not only reduce costs, but also enhance the quality of life of many people.

I thank you, Mr. Chairman, and we at AARP stand ready to be of any assistance and to work with you in any way that we can.

[The prepared statement of Monroe T. Gilmour follows:]

STATEMENT

of the

American Association of Retired Persons

on

DRUG MISUSE AMONG THE ELDERLY AND ITS IMPACT ON COMMUNITY-BASED CARE

Presented By

Dr. Monroe Gilmour
Member of the AARP Board of Directors

before the

House Select Committee on Aging
Subcommittee on Human Services

April 19, 1989

Good morning Mr. Chairman. My name is Monroe Gilmour and I serve on AARP's Board of Directors. AARP is pleased to have the opportunity to discuss the problem of mismedication among older adults. We believe this is a critical issue--both in terms of cost and quality of care--and we commend the Subcommittee for holding these timely hearings.

The Extent of the Problem

The problems resulting from mismedication have been clearly documented, and there is reason to believe that the statistics in fact underestimate the problem. As the recent HHS Inspector General's report indicated, in 1985, over a quarter of a million older adults were hospitalized for adverse drug reactions. Thousands more suffer serious mental impairment as a result of inappropriate medication, and an estimated two million elderly are either addicted or at risk of addiction due to overprescribing of tranquilizers and sleeping pills. It is not surprising that the problem of over-medication and mismedication has been dubbed by some as "America's other drug problem". The human cost of this problem cannot be measured and the financial cost of adverse drug reactions alone is estimated to be as much as $7 million per year.

There are numerous anecdotal accounts of older persons modifying their prescription drug regimens because of financial constraints. In 1986, an AARP national telephone survey found that the second most frequently cited reason given by older Americans for not getting a prescription filled as ordered by their doctors was the cost of the drug. The high cost of drugs has clearly gained in prominence as a reason for non-compliance with prescribed drug regimens. A prior survey, in 1982, found that cost ranked fourth. The new Medicare catastrophic drug benefit will help to ameliorate some of the non-compliance caused by high costs, but, as you know, the $600 annual deductible will still present a barrier to access for needed medicines for many older Americans whose incomes are above poverty but not adequate to pay the high cost of prescription drugs.

Factors Underlying the Problem

Mismedication can result from any one of a number of factors. The physiological changes that accompany the aging process--for example, decrease in the efficiency of liver and kidney function--make elderly persons much more susceptible to adverse reactions caused by drug toxicity. Yet, many of the drugs used to treat conditions common among the elderly were not clinically tested on older persons. As a result, very few drugs have specified dosage schedules that are appropriate for elderly patients. At best, the practitioner is advised to "use with caution in elderly or debilitated patients." While such advice may prompt physicians to monitor elderly patients more closely, it is not an adequate substitute for clinically tested safe dosage schedules.

Another factor underlying the problem of mismedication is poor prescribing practices. Such practices reflect the failure of medical education to include sufficient course work in both pharmacology and geriatrics. Compounding this problem is the lack of continuing education in these two areas. Studies have shown that promotional materials from pharmaceutical companies are often the primary source of drug information for practicing physicians.

A third factor contributing to mismedication is the lack of counseling by health professionals. Counseling by doctors and pharmacists is especially important for elderly patients, yet AARP surveys show that, overwhelmingly, patients are not being counseled on even the most elementary aspects of their drug therapies. A medication label which states "Take as directed" is not sufficient instruction for an elderly person who may be taking four or five medications prescribed by multiple physicians. AARP has long advocated that patients be provided with "patient package inserts" (PPI's), written in lay language, which would accompany every prescription dispensed. In this way, basic information such as directions for use, contraindications, and anticipated side effects would be available to the patient, whether or not they had been counseled verbally. Although the new Medicare catastrophic drug benefit stipulates that pharmacists offer counseling to beneficiaries on their drug therapies, AARP maintains that mandatory patient package inserts are necessary to assure that all patients receive basic information. A written format also allows the patient to access vital information whenever they need it and at a time when they can understand it best. A person experiencing stress during an office visit may not accurately remember the doctor's instructions once he or she returns home. When purchasing a prescription, a person may not want to take up too much of the pharmacist's time if several customers are waiting in line. Additionally, counseling at a pharmacy counter offers little or no privacy. Hence, persons may feel uncomfortable discussing their medications with the pharmacist under such circumstances.

AARP has great hopes that the Medicare catastrophic drug benefit will decrease the incidence and severity of mismedication among the elderly. The drug utilization review system that will be implemented has tremendous potential if used to its greatest capacity. It is imperative that the system be designed to scan each patient's drug regimen to detect duplicative medicines, contraindications, avoidable adverse drug reactions and other negative aspects of drug therapy, before any new medication is dispensed. We strongly advocate that Congress conduct careful oversight to ensure that these functions, which address quality, are not compromised in the implementation phase of the new legislation.

Since quality assurance and cost containment are often viewed as conflicting goals, it is important to remember that reducing the incidence of mismedication will both increase the quality of care provided to the elderly and reduce the costs associated with mismedication.

Mr. DOWNEY. Thank you, Dr. Gilmour.

I have one question for the panelists, and then, if I am not joined by another of my majority colleagues, I'm going to recess the hearing for 20 minutes. I apologize to Doctors Webb, Beary and Fair. I will be back directly. I will recess the hearing in a few minutes for 25 minutes.

Dr. Williams, can you elaborate for me any concerns you might have on the FDA's failure to publish guidelines and implement them?

Dr. WILLIAMS. Well, we have worked with the FDA and encouraged them to bring out these guidelines, pointing out the need for them. With the deficiencies in testing in older people for some years, I have been very glad to see that they've been moving on this. I would like to see them out as soon as possible.

Mr. DOWNEY. The Inspector General's report, and Dr. Lipton's testimony, referred to the illness medication spiral or the polypharmacy spiral. Is that the correct pronunciation of—

Dr. LIPTON. My colleagues in medicine would rather it be called the polymedicine spiral.

Mr. DOWNEY. The polymedicine spiral.

Dr. LIPTON. Yes.

Dr. WILLIAMS. Either one.

Dr. LIPTON. Either one.

Mr. DOWNEY. Either one will do. Okay.

How prevalent a problem do you feel this is and why, when doctors see their patients are taking a number of drugs, why don't they stop and do the reevaluation? Dr. Gilmour, if you could address that as well as Dr. Williams, I would appreciate it.

Dr. WILLIAMS. I guess I would say it is a very common problem, and it's a complex problem, in that for one thing patients do go to more than one doctor and they may not know who has prescribed what.

But, in addition, I would have to say that I don't think doctors often take enough time to try to be sure they have identified all the medications a patient is taking. I think it is a matter that we should expect professionally of our colleagues, to do exactly that. So I think it's a matter of professional discipline as well as being more informed, to be sensitive to these issues. I think it's a real challenge.

Dr. GILMOUR. I would agree thoroughly with that. Also, patients don't consider medicines they have bought at the drug store themselves as medicines. They don't report those to the doctor, so that may be of some significance.

Mr. DOWNEY. You mean over-the-counter sales?

Dr. GILMOUR. Yes, over-the-counter medicines.

Dr. WILLIAMS. Just one final comment. I think the pharmacist can be very helpful in detecting such phenomena if they have the opportunity to keep a record on the range of medications that a patient is taking.

Mr. DOWNEY. Also, the Inspector General noted that there are a number of variables that could predict noncompliance with drug therapy, and I believe Dr. Lipton referred to this in another way when she cited social isolation as one factor.

Shouldn't doctors be aware of this? I mean, I guess part of the question is shouldn't doctors do a better job?

Dr. Gilmour. Doctors should be. But getting the information, a patient doesn't even remember when he comes to a doctor's office.

I have a "pie in the sky" idea. I would like to see every patient carry with him not only his Social Security card and his drivers license and his ID card, but a list of his medications. If he had that, then wherever he went he would be safe. A doctor has a hard time getting that information. A patient doesn't remember when asked what he's taking.

Mr. Downey. Dr. Lipton?

Dr. Lipton. I think ideally, yes, Congressman Downey, physicians should be aware. But this speaks to the issue that I addressed in my testimony. There is very little attention in medical school curricula to the risk factors that make the elderly particularly vulnerable to noncompliance, one of which is social isolation. But there are many other variables as well. Nor is there any attention on how to deal with this problem once it is detected.

Mr. Downey. Let me just thank the members of the panel. You have been very helpful to us. We appreciate your traveling great distances to get here and to offer your wisdom. This is a matter of deep concern and interest to those of us who sit on the Aging Committee and to those of us who also sit on the Ways and Means Committee, who deal with this subject in a more fundamental way. Thank you very much.

Dr. Lipton. You're welcome.

Dr. Gilmour. Thank you.

Mr. Downey. Again, my apologies to the next panel. I shall return in 20 minutes time. The subcommittee is adjourned.

[Whereupon, the subcommittee was in recess.]

Mr. Downey. The subcommittee will come back to order. I apologize to Dr. Webb, Dr. Beary and Mr. Webb for keeping you longer.

Dr. Webb, if you would begin, please.

PANEL TWO, CONSISTING OF: C. EDWIN WEBB, PHARM.D., DIRECTOR OF PROFESSIONAL AFFAIRS, AMERICAN PHARMACEUTICAL ASSOCIATION; JOHN F. BEARY, III, M.D., SENIOR VICE PRESIDENT, SCIENCE AND TECHNOLOGY, PHARMACEUTICAL MANUFACTURERS ASSOCIATION; AND RUSSELL B. FAIR, THIRD PARTY SUPERVISOR, PHARMACY LIAISON, GIANT FOOD, INC.

STATEMENT OF C. EDWIN WEBB

Dr. Webb. Mr. Chairman, Thank you very much for the opportunity to appear before the subcommittee. My name is Ed Webb. I am a pharmacist and Director of Professional Affairs with the American Pharmaceutical Association, which is the national professional society of pharmacists.

I am pleased to appear before the committee today to share our perspective on issues of medication use and misuse in the elderly. In particular, we would like to focus our comments on aspects of the recently released draft report of the Office of the Inspector General concerning Medicare drug utilization review.

APhA's support for a prescription drug component within the Medicare Catastrophic Coverage Act of 1988 was, and is, predicated on our firm belief in the value of comprehensive pharmacy services and prescription drug products in the care of patients. In no group is this value more evident than in the elderly.

Pharmacy has evolved over the past 2 decades into a profession that is focused not only on medication dispensing and control, but on assuring the quality and appropriateness of drug therapy as well. Pharmacists are involved in the care of elderly patients in virtually all settings.

You have already heard from several other witnesses today regarding the extent and potential sources of medication-related problems in the elderly, so I won't go into some of those comments, although in our testimony we do outline some of those and would like for them to be submitted for the record.

I would simply reemphasize those points and to note that pharmacy practitioners and researchers have been among the leaders in studying and reporting on these problems in the literature.

APhA is very pleased that the OIG draft report emphasizes the professional judgment of the pharmacist as a central element in the process of effective drug use and evaluation in the elderly. I regret that Dr. Young took away his visual. I was going to jump at it with a magic marker and add in the pharmacy profession in that triangle because I think it's very important to note that.

Mr. Downey. Make it sort of a rectangle then.

Dr. Webb. That's right. As the report notes, significant improvements in the overall quality of drug therapy regimens can be achieved when pharmacists, prescribers and patients communicate effectively with each other.

For the sake of time, I will not review all of our entire set of comments on the OIG draft report. They are included in our written statement. Nevertheless, I want to emphasize the APhA does support two of the major tenets of the draft report—that is, improvements in the rational, effective and safe use of medications by the Nation's elderly are both desirable and necessary, and that efforts to evaluate drug usage in the Medicare population should focus on the promotion of both quality of care as well as concerns about program costs and program integrity.

I would like to take just a minute to draw some important distinctions in some of the drug regimen review terminology that's been used outlined in the OIG report, which are currently the subject of intense interest at HCFA as they begin implementation of the Medicare Catastrophic Drug Program.

Prospective review, in our view, is a patient-specific and prescription order-specific review process that involves consultation and discussion with patients prior to the dispensing of a drug product. On the other hand, retrospective review is a post-dispensing review that serves to analyze trends and identify more general and global patterns of medication use and misuse.

APhA is supportive of the principle that prospectively performed drug use evaluation is an effective approach to identifying and preventing medication problems in the elderly or any other patient population.

Many pharmacists are routinely performing this important activity in their daily practice today, using sophisticated patient profile and drug interaction databases as a part of that practice. APhA continues to provide educational and other services to pharmacists to enhance their skills in this area.

It is important to note that a recent study in one of the computer trade magazines indicated that approximately 75 percent of the community-based pharmacies in the country right now are already computerized and have substantial drug interaction and drug intercompatibility database capabilities. It is important to know that that action exists out there at the present time, and I think one of the other speakers will address some of that.

APhA emphasizes, however, that it is incumbent upon those who pay for service to ensure that reimbursement for cognitive services appropriately reflects the time and expertise required to perform those services.

Consider the case of a prescription order that the pharmacist determines is either a duplication of current therapy or will interact adversely with current therapy that the patient is already on. The pharmacist will commonly consult with the prescriber and review the problem, with the possible outcome that the prescription order is voided. The pharmacist will then review that change and discuss it with the patient. This activity occurs every day in a variety of settings, not just community settings, but hospital settings as well. Yet the reimbursement formulas for drug programs in our country are almost exclusively tied to the dispensing of the drug product, not to the provision of this type of clearly beneficial service. To us, recognition of the value of the cognitive services that pharmacists provide and should provide, through appropriate changes in reimbursement methodology, is essential.

APhA is also concerned that some of the current efforts within the Health Care Finance Administration to incorporate a rudimentary clinical database, along with the point-of-sale electronic claims system for processing claims, is ill-conceived. Based on information that we have obtained to date in meetings with HCFA staff, we question the ability of the POS system being planned by HCFA to function as a valid clinical data resource for pharmacists without extensive testing. APhA contends that it will have insufficient operating capacity, speed and technical and professional sophistication to support the kind of comprehensive prospective DUE called for in the OIG draft report. The report itself notes that such a system should be sufficiently comprehensive and compatible with existing systems, which I have previously described, so that pharmacists are not required to operate separate systems. APhA believes that this very appropriate and reasonable recommendation is unlikely to be met with the system currently being contemplated.

Finally, the report calls for establishing a blue ribbon panel to perform various functions related to improving medication use in the elderly. While we certainly support this, we would like to make the following additional points:

In calling for the panel to develop criteria for DUE to be utilized throughout the country, we urge the panel be encouraged to utilize the expertise and experience of the many successful State and regional DUE programs already in existence.

Also, in calling for the panel to make curricular recommendations regarding geriatrics and pharmacology, the report should expand its focus beyond just medical schools to include all appropriate health professional schools, including schools and colleges of pharmacy. APhA is among several pharmacy professional associations which met last month to begin to examine the current status and future directions for geriatric education and training for pharmacists.

We are very gratified by the high level of interest in Congress on the subject of appropriate medication use in the elderly population, and we stand ready to work with you in this important area. We thank you for the opportunity to be with you today.

[The prepared statement of C. Edwin Webb follows:]

Statement
# of the
American Pharmaceutical Association

The National Professional Society of Pharmacists

MEDICATION USE AND MISUSE IN THE ELDERLY

PRESENTED IN CONJUNCTION WITH THE HEARING

HELD BY THE

HOUSE SELECT COMMITTEE ON AGING

SUBCOMMITTEE ON HUMAN SERVICES

WASHINGTON, D.C.

APRIL 19, 1989

SUBMITTED BY

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Mr. Chairman, my name is Edwin Webb. I am a pharmacist and the Director of Professional Affairs of the American Pharmaceutical Association (APhA), the national professional society of pharmacists. I am pleased to appear before the committee today to share our perspective on issues of medication use and misuse in the elderly. In particular, we would like to focus our comments on aspects of the recently released draft report of the Office of the Inspector General (OIG) concerning "Medicare Drug Utilization Review".

APhA's support for a prescription drug component within the Medicare Catastrophic Coverage Act of 1988 was, and is, predicated on our firm belief in the value of comprehensive pharmacy services and prescription drug products in the care of patients. In no group is this value more evident than in the elderly.

Pharmacy has evolved over the past two decades into a profession that is focused not only on medication dispensing and control, but on assuring the quality and appropriateness of drug therapy. Pharmacists, as the health care system's most readily accessible professional, are involved in the care of elderly patients in all settings. For example, many elderly patients benefit from the active role of the pharmacist in the drug regimen review process in skilled and intermediate long-term care facilities. Pharmacists are specifically recognized by the Health Care Financing Administration (HCFA) as the health professional responsible for drug regimen review in this setting. This important role serves to assure therapeutic appropriateness while at the same time identifying such drug-related problems as therapeutic duplications, drug-drug interactions, adverse effects and other drug-related problems. Integral to the success of this role is an effective working relationship with other health professionals involved in the care of these patients.

As the Committee is aware, the nation's elderly population, which is steadily increasing, is a major consumer of health care services. With regard to medication use:

- Those over 65 years of age consume slightly more than 30% of the nation's prescription medications, although they represent only 12% of the total population.[1]

- A 1987 study at the University of Michigan College of Pharmacy has shown that 15% of the elderly population take four or more medications concurrently.[2]

- It is estimated that 70% of all medications prescribed for the elderly are for chronic therapy, and that 30-40% of the elderly population have more than one chronic disease.[3]

The potential problems associated with use of prescription drug products, particularly among the elderly, can occur in a number of different ways:

(1) higher doses are prescribed when a lower dose would provide the same benefit with lower risks;

(2) medications with greater potential for adverse reactions are prescribed when a drug product with fewer potential side effects would be as effective;

(3) the combination of medications in the patient's regimen produces adverse interactions;

(4) physiologic or pathologic changes in the elderly patient may predispose them to particular drug therapy problems; and

(5) a particular medication prescribed is unnecessary or inappropriate, either because the patient's condition has been misdiagnosed or because non-drug therapy could be substituted;

APhA is pleased that the OIG draft report emphasizes a central element in the process of effective drug use and evaluation in the elderly -- the professional judgment of the pharmacist. As the report notes, significant improvements in the overall quality of drug therapy regimens can be achieved when pharmacists, utilizing sufficiently complete and comprehensive information, communicate with prescribers and patients.

APhA supports the two major tenets of the OIG draft report:

(1) improvements in the rational, effective and safe use of medications by the nation's elderly population are both desirable and necessary;

(2) efforts to evaluate drug usage in the Medicare population should focus on the promotion of quality of care as well as on concerns about program costs and integrity.

In 1988, the APhA House of Delegates adopted several specific policies related to drug usage evaluation (DUE). This terminology is used by APhA to describe a structured, ongoing, organizationally authorized quality assurance process designed to ensure that medication is used appropriately, safely and effectively. Because the term drug utilization review (DUR) is sometimes associated purely with quantitative and cost assessments of drug use, the acronym DUE is used by APhA to emphasize both the qualitative as well as quantitative aspects of appropriate medication usage.

In general, APhA believes that the OIG draft report is a reasonable initial analysis of the complex issues surrounding medication use in the elderly. The report is generally well referenced. Nevertheless, APhA has urged that the final report be meticulously reviewed to document the sources and quality of data used to support the quantitative estimates of mismedication, hospitalizations due to adverse drug reactions and other problems of concern in the report. This is particularly true because this report, in its final form, will likely serve as a benchmark for future evaluation of the problems described.

APhA is supportive of the principle that prospectively performed DUE is an effective approach to identifying and preventing medication problems in the elderly, or any other, patient population. Standards of practice of the profession, jointly developed by APhA and the American Association of Colleges of Pharmacy (AACP), specifically address the role of the pharmacist in identifying potential drug therapy problems. Many pharmacists are routinely performing this important activity in their practice, and APhA continues to provide educational and other services to pharmacists to enhance their skills in this area.

APhA emphasizes, however, that it is incumbent upon those who pay for services to insure that reimbursement for these cognitive services appropriately reflects the time and expertise required to perform them. Consider the case of a prescription order that the pharmacist determines is either a duplication of current therapy or will interact adversely with current therapy. The pharmacist will commonly consult with the prescriber and review the problem, with a possible outcome that the prescription order is voided. The pharmacist will then review the changes with the patient as well. Such activities serve both the patient's interest and the payer's interest. This activity occurs every day in most pharmacy practice settings. Yet reimbursement formulas are tied almost exclusively to the dispensing of a drug product, and not to the provision of this type of clearly beneficial service. Recognition of the value of the cognitive services that pharmacists provide, through appropriate changes in reimbursement methodology, is essential.

APhA agrees with the report that the ability of pharmacists to effectively perform DUE depends on an accurate and complete medication data base. For that reason, APhA is particularly concerned that some of the current efforts within the Health Care Financing Administration (HCFA), in implementing the Medicare Catastrophic Coverage Act, to incorporate a basic clinical data base along with the point-of-service (POS) electronic claims processing system are ill-conceived. Based on information obtained to date in meetings with HCFA staff, APhA questions the ability of the POS system being planned by HCFA to function as a clinical data resource for pharmacists without extensive testing. APhA contends that it will have insufficient operating capacity, speed and technical and professional sophistication to support the kind of comprehensive prospective DUE called for in the draft report. The draft report itself notes that the system should be sufficiently comprehensive and compatible with existing systems so that pharmacists are not required to operate separate systems. APhA believes that this very appropriate and reasonable recommendation is unlikely to be met with the system currently being contemplated.

APhA has strongly recommended to HCFA that it consider the development of demonstration projects to examine the feasibility of adding clinical information capabilities to the POS system, only after it has become fully operational in its primary purpose of data submission and claims processing. We are therefore gratified to see a similar call for such demonstration projects in the draft report.

APhA supports the report's call for the availability of funding for research and demonstration projects that will test DUE interventions and evaluate their relative benefits and costs. APhA also believes that studies should be performed to examine the contributions of effectively managed drug therapy to overall cost reductions within the Medicare system, i.e. reduced hospitalization and other non-drug expenditures.

The report calls for establishing a blue ribbon panel to perform various functions related to improving medication use in the elderly. While generally supportable, APhA would make the following additional points:

(1) in calling for the panel to develop criteria for DUE to be utilized throughout the country, APhA urges that the panel be encouraged to utilize the expertise and experience of the many successful state and regional DUE programs already in existence. APhA has offered to assist in identifying and providing experts in this area.

(2) in calling for the panel to make curricular recommendations regarding geriatrics and pharmacology, the report should expand its focus beyond medical schools to include all appropriate health professions schools, including schools and colleges of pharmacy. APhA is among several pharmacy professional associations which met last month to examine the current status and future directions for geriatric education and training for pharmacists.

Finally, APhA is supportive of the report's suggestion that guidelines be developed to ensure appropriate clinical testing of new drugs in the elderly, particularly with those drugs likely to have their primary use in that population.

APhA is gratified by the high level of interest in Congress on the subject of appropriate medication use in the elderly population, and stands ready to work with you in this important area. Thank you for the opportunity to be with you today.

REFERENCES

1. Pequet BK et.al. Prescription drugs: a survey of consumer use, attitudes and behavior. AARP Publications, 1986.

2. Shimd LA and Ascione FJ. Unpublished data. University of Michigan College of Pharmacy, 1987.

3. Lamy PP. Drug use and the elderly. Testimony - Senate Special Committee on Aging, July 1987.

Mr. DOWNEY. Thank you, Dr. Webb.

Dr. Beary.

STATEMENT OF JOHN F. BEARY, III, M.D.

Dr. BEARY. Thank you, Mr. Chairman. It is evident from the testimony of earlier witnesses that the committee has identified a subject that is extremely important in American health care, and there have been a lot of good ideas advanced on different dimensions of it that we need to be attentive to.

I am senior vice president for science and technology at PMA, and I am also Board certified in geriatric medicine and rheumatology and continue to practice part time, so I will contribute my clinical perspective as well today.

I will summarize here in the interest of time.

We recently did a series of surveys showing the industry's commitment to finding new medicines for the elderly, and I have included some material in my statement. Our last survey showed that there were 221 medicines under development to treat 23 common diseases that are prevalent among the elderly, including the Alzheimer's problem that Dr. Williams was quite concerned about today. This amounts to $3.6 billion in research on diseases of the aging, so we do have a significant interest and commitment to these problems.

One of the topics that came up several times today I will just take a moment to deal with. Because of the industry's role in discovering and developing medicines for older people, we are quite concerned that information about the R&D process be accurately portrayed. I draw your attention to my chart there, a copy of which is in my statement, to let you read the smaller print easier. But it shows what happens as you go from a compound in the laboratory through human testing, through FDA review, into manufacturing and into the pharmacy.

We were particularly concerned about the part of the IG report that asserted that clinical studies on new drugs in older people are typically performed on "healthy young adults for a short period of time." The only thing I could figure out was that he was either talking about pre-1983 matters—and I wasn't around at that time, but I think geriatrics is a relatively new field, as we heard the first certification exam was just given last year. It's really been sort of the decade of the '80s that interest in this subject has increased, since we've all looked at the demographics and have seen what is here and what's going to come and so on.

The only other thing I could figure out was perhaps someone had gotten phase one of three phases confused with being the whole process. Phase one I think it's worth just taking a moment—Well, there are three phases. Roughly, you spend a year on phase one, a year on phase two, and 3 years on phase three of human studies. So the goal of all of that is, once you have a compound that in an animal model of some sort shows some activity, you want to see if it's safe in people and does it work, and if so, the FDA then reviews it and approves it for market, if appropriate.

Well, in phase one you study 50 healthy young people, and the idea there is you're just trying to get a dosage range. You don't want to take someone who may be more susceptible to kidney or liver problems and do those simple elementary tests there. Because about one-third of those drugs will never be seen again. They're going to have something that's just a little too toxic to continue testing with, or they don't work, just a variety of things. So in there you look at some pharmacokinetic issues, as we were talking about today.

Pharmacokinetics basically talks to what happens to the drug in the body, and there are four phases—absorption, distribution of the drug in the body, metabolism, what's done to it in the liver, and then excretion, how does the body get rid of it, through the bile, through the kidneys, what have you. But, given that preliminary information, you can then design proper trials that have large numbers of elderly in them and study the disease in question. So if you're going to study angina, if you're going to stay Alzheimer's, hopefully your not looking at people your age and my age. You're going to have to look at these people age 60 and over where the bulk of this disease is.

So phase two will have a couple hundred, 300 people in it, and phase three will have about 3,000 people in it. As we heard from looking at the drugs approved in '88, as I recall hearing, about 30 percent of those people in phase three were old people, as they should be, however one defines that.

So I did want to take just a moment to make it clear that we do disagree with that. I think when we responded to Mr. Kusserow, I think he has taken that into account and we tried to lay out the nature of our concern. It is a very complicated situation.

We have heard from the FDA about the status of the guidelines and so forth. I would make a point that the resource situation is a tough one. Most people think the Parklawn building is the FDA building. It isn't. They're only 45 percent tenants out there, and that's why the average worker is in an 8x10 foot room—for those of you who have been there—with documents stacked to the ceiling.

These NDAs, the big document that summarizes all the scientific data for reviewing a drug, are 100,000 pages. And then, as they're reviewing that, there are INDs, which is at the start of the process when you first study a drug, you put a document called the IND. But when that roars on to your desk and you've got a limited amount of time to deal with that. So the point is the space thing is abysmal and really needs some attention.

The salary situation, again, markets are markets, and to get the people they need at the FDA—physician reviewers I'm focusing on here—is a very, very tough sale. Washington, as I have no need to tell those in the room, is one of the highest cost-of-living places in the country. So if you're trying to raise a family and you're going to be buying a house, in today's market you're going to be looking at Point Lookout, MD to get your house, and you had better just sign a pledge not to have any kids while you're here because that's going to put your budget in a disaster mode, too. So these things certainly need some attention. Because if you don't have the resources to do the work load, it is just demoralizing.

Medication management in the elderly, a complex, mutli-factorial matter. I have listed some things that manufacturers do for involvement in this process.

In terms of patients, I will take just a moment here—and this is from a practitioner's view—and share this with you.

Patients need to have a primary care doctor to coordinate their care and keep a master drug list. It would be nice if the specialist were interested in this, but they're never going to be. They're going to want to check the heart, do their thing, and they're not trained, and probably never will be, to do the things a generalist will do.

Even in a sophisticated group like this, there are probably some people in this room who don't have a primary care doctor themselves. A primary care doctor is a general internist, a family practitioner—a geriatrician for adults I'm talking about. Primary care is defined as coordinated, comprehensive, continuous care. You think of delivering medical care like an orchestra. Somebody has to be the conductor, so that the horns play when they're supposed to and the strings play, and you get music, you don't get noise.

Well, I will run into charts where somebody—I'm trained in geriatrics, so I'm obviously trained to look for this and try to sort it out and correct it when I do. But someone who has been seeing several specialists, nobody has a clue to what's going on in the various drug lists, if anybody is keeping one at all. I'm generalizing a bit, but it is such a simple thing, but it is so important on whether things work or not that we really do need to give attention to it. So what it basically boils down to, it is better to be organized than disorganized.

Noncompliance we have talked about. In terms of physicians, there is a body of knowledge on geriatric medicine that is evolving. The first certification exam was just a year ago, as you heard. I heard a lot of questions about geriatric education, which I think is worth spending just a moment on.

If you look at medical education—and here I'm going to focus on that since I'm most familiar with it. We do need to be attentive to the pharmacy education needs, as other witnesses have mentioned, because health care is delivered by a team. But you can think of it as undergraduate medical education, UGME medical school, GME, graduate medical education residency training, and CME, continuing medical education. It's a spectrum.

If you think about the 4 years of medical school, I encourage you not to put all your eggs in that basket. Geriatrics is important, but remember, their minds are absolutely being crammed with an explosion of things, most of which they don't remember 6 weeks after they take the test. That's just a reality of learning.

Now, you in Congress obviously have to be tremendous generalists. It would be like if you had to have a course on, just to be arbitrary, in a year on defense strategic policy, nuclear physics, energy things, all these technical things, on and on. You would get something out of it, but you're not going to take enough away to say, "Gee, that's it, I've got it down. I can relax." Furthermore, in 5 years, 50 percent of what you heard will be obsolete, and who knows which 50 percent. So you have to think about that.

In residency, you actually remember better what you're doing because you're applying it. That is why small group instruction works better. I used to work in a dean's office, so I have a sense of some of the curricular things. But that's why small group instruction works better and why, when you have hands on practical things, and you're supervised as you do this—I mean, there is a junior resident and a senior resident and a chief resident and attending, so someone is not just, in vacuo, trying things out. But you get a problem, you think about it, you say what you're going to do, and your superiors tell you if that's a smart idea or not. Then you apply it and probably remember it forever, particularly if it's something that's kind of a common problem. So that approach to education certainly beats what you can do as a medical student, not minimizing that things have to happen there, too.

Then you face the issue of, well, the major part of your practice 4 years or so, you know, you're out there by yourself. So how do you have objectives to make sure people get updated in things. So I suppose the major advice I would give is to know exactly what your objectives are and think of it in that spectrum, so that you get the results you would intend to.

Some of the principles of geriatric medicine I would emphasize are, one, using nondrug treatment such as weight loss and exercise, where appropriate; two, use as few drugs as possible in the elderly, and where it's possible, try to use one drug to treat two problems. One of my major jobs is to try to take some 14 drug lists I inherit and whittle it down to five or six rational things targeted on the problems that take into account really the hundreds of variables you have to consider in people with several serious illnesses.

For example, in some patients it might be appropriate to use as calcium channel blocker to treat both hypertension and angina. You use one thing to do two jobs.

Third is the "low and slow" rule. If a medication is necessary, start treatment at the low end of the dosage range in then increase the dose slowly.

Fourth, once you prescribe, keep monitoring the patients carefully. Keep in mind the physiologic changes we have heard about earlier today, like renal function, age related changes in liver function, changing in how the body itself is composed. It is bad news to all of us, but as we get older, we're going to have more fat and less water, decreased lean body mass, so you've got to think of all those things when you're prescribing.

In regard to the pharmacist, people don't take as much advantage as they should to the services provided. You're going to hear some more about that. Indeed, they should be on the pyramid right there.

The point about cognitive services is well taken. You have a patient in front of you who might not see too well, can't hear too well, and you've got to repeat everything three times in a loud voice while 10 other people are backing up at the counter on a complicated issue. You sort it all out. It's going to involve a phone call, maybe to two doctors, maybe to one, and so on. So it is easy to say these things should happen, but please realize they'll take a lot of time and somebody has to think about where the compensation for that will come from. I think that has been a neglected point as people have thought about the role of pharmacists. I agree with Dr. Webb's comment there.

In regard to drug utilization review, I will let my statement speak for itself.

Labeling of medications for the elderly is an issue that has come up here today. I would say to further enhance the value of label information for physicians and patients, we would be pleased to work with FDA to improve the dosage and administration part of the product label as it pertains to the elderly.

The labels have become a very complex document in recent years. More of it is written by attorneys than it is by scientists, so I just know when I'm prescribing myself, I look at that dosage and administration part. Nine times out of 10 it's the first part you look at. You look at other parts now and then as well, depending on how familiar you are with the drug. But that part you kind of know what you're going to find there. So if you need information to treat a special population like the elderly, you know, why not make it easy to find there. What is the dose for the elderly or—

Mr. DOWNEY. Dr. Beary, I don't mean to be rude, but you're going to have to summarize the rest of your testimony, if you could.

Dr. BEARY. All right. I'm really at the end of my statement.

I would just summarize by saying that many of these health problems of the elderly are best treated by prescription drugs that can keep people out of the hospitals, reduce the need for costly surgery, and allow older citizens to remain independent and productive longer. We will work with all of you to achieve those aims.

Thank you.

[The prepared statement of John F. Beary, III follows:]

Statement Pharmaceutical Manufacturers Association

JOHN F. BEARY, III, M.D.
SENIOR VICE PRESIDENT, SCIENCE AND TECHNOLOGY

PHARMACEUTICAL MANUFACTURERS ASSOCIATION

ON

MEDICATION AND THE ELDERLY

FOR THE

SUBCOMMITTEE ON HUMAN SERVICES

SELECT COMMITTEE ON AGING

U.S. HOUSE OF REPRESENTATIVES

APRIL 19, 1989

Mr. Chairman and Members of the Committee:

The Pharmaceutical Manufacturers Association (PMA) appreciates the opportunity to appear before the Committee today to discuss the January 1989 Report of the Inspector General (IG Report) of the Department of Health and Human Services entitled "Medicare Drug Utilization Review" relating to medication and the elderly. PMA is a nonprofit scientific and professional organization of more than 100 member companies that discover, develop and produce most of the prescription drugs used in the United States.

I am Senior Vice President for Science and Technology at PMA and am board certified in Geriatric Medicine and Rheumatology. In addition to my PMA duties, I see patients regularly and will contribute my clinical perspective as well in this testimony.

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The IG Report focuses attention on the need to ensure that elderly people both receive necessary medications and use them appropriately. The Report reviews medication problems in the elderly and comments on Medicare Drug Utilization Review (DUR). In the interest of time, I will only comment on the major issues raised in the IG Report.

The Pharmaceutical Manufacturers Association recently completed a series of surveys that shows the research-based pharmaceutical industry's enormous commitment to discovering and developing medicines that will help older people live longer, more productive lives. The results showed that the industry is testing 221 medicines to treat 23 diseases prevalent among older people (Appendix 1). The research projects include 87 on cardiovascular disease, 65 on cancer and 69 on arthritis, Alzheimer's and other diseases that strike the elderly.

The pharmaceutical industry will invest an estimated $3.6 billion in research on diseases of the aging in 1989 -- approximately half of its projected $7.3 billion research and development budget for this year.

Because of the industry's role in discovering and developing medicines for older people, we are very concerned that information about the research and development process be accurately portrayed. PMA is particularly concerned about the IG

Report's assertion that clinical studies on new drugs for use in older people are typically performed on healthy young adults for a short period of time. Healthy young adults are used in only the first phase of human testing which is appropriate. Human testing is a multiphase process that takes an average of 6 years to complete (Figure 1). In subsequent phases, new drugs for the elderly are typically tested for years on large numbers of older people, because they are the people with the conditions that the drugs are intended to treat. Appendix 2 contains further information on the drug development process and drug labeling.

My own recent discussions with industry R&D leaders confirm that we study numerous elderly people when a new drug is developed. FDA has conducted a recent survey on this subject and we are awaiting the results.

Medication Management in the Elderly

Providing necessary medication for the elderly is a complex, multifactorial matter that involves manufacturers, patients, physicians and pharmacists.

Manufacturers

Pharmaceutical manufacturers contribute to proper use of medication in the elderly by extensive testing of new medicines in animal and human subjects prior to marketing approval by the FDA; development of product labeling with the FDA that provides physicians with information needed to prescribe a medication appropriately; educational efforts by the sales force to make physicians aware of products and how to use them properly; support of patient information programs via membership in the National Council on Patient Information and Education; and documentation of adverse reactions in the post-marketing period by participation in pharmacoepidemiology programs.

Patients

Patients need to have a primary care doctor to coordinate their care and keep a master drug list. Primary care for adults is delivered by general internists, family practitioners, and geriatricians. Primary care is defined as provision of coordinated, comprehensive and continuous care.

An old person may have many diseases, see several physicians and receive several prescription drugs. Many people do not have a primary care doctor and thus are at increased risk for adverse drug reactions because of this disorganization.

Non-compliance with medication instructions results in problems of both undermedication and overmedication. The noncompliance problem is well known to clinicians and is deserving of continuing research efforts to ameliorate it.

Physicians

A body of knowledge on geriatric medicine has evolved in recent years. Indeed, the first certification exam in Geriatric Medicine was given only one year ago in April 1988. Medical education authorities must emphasize programs that ensure that physicians are aware of the following principles of geriatric medicine.

1. Use nondrug treatments such as weight loss and exercise where appropriate.
2. Use as few drugs as possible in the elderly. Where possible, try to use one drug to treat two problems. For example, in some patients it may be appropriate to use a calcium channel blocker to treat both hypertension and angina.
3. Low and slow rule. If a medication is necessary, start treatment at the low end of the dosage range and increase the dose slowly.

4. Monitor patients carefully, keeping in mind physiologic changes in the elderly such as declining renal function, age-related changes in liver function, and changes in body composition related to increased body fat, decreased body water, and decreased lean body mass.

Pharmacists

Patients should take advantage of medication counseling services available from their family pharmacist. Pharmacists have the training and modern information management tools to assist patients in taking their prescriptions safely and effectively.

The Medicare Catastrophic Coverage Act of 1988 recognizes the important role of pharmacy and specifically provides for reimbursement for their important services.

Drug Utilization Review (DUR)

Regarding drug utilization review, PMA supports the DUR provisions of the 1988 Medicare Act and appropriate DUR programs at the state Medicaid level. Accordingly, there are several points about DUR that we wish to emphasize:

1. PMA believes that the critical objective associated with drug utilization review is to improve the quality of care. Although DUR has the potential to reduce drug program costs, the exact amount is not certain. In fact, DUR will likely identify cases where there is a serious "under-utilization" of prescription drugs. Given the well recognized cost-effectiveness of modern drugs, it is therefore appropriate in DUR to focus on the improved quality and savings for overall health care costs that result from the proper use of pharmaceuticals.

2. PMA believes that the objective of maintaining program integrity should be a key component of Medicare DUR. The IG's Report asserts that Medicaid DUR policies have "limited applicability" for Medicare because of their emphasis on fraudulent or abusive activities. PMA believes the value of this area of DUR should not be underestimated. Instances of fraud and abuse may be quite costly, are easily identifiable and may have a major impact on the integrity of the Medicare program.

3. PMA believes that the IG Report may be overly optimistic about the capabilities of prospective DUR. Experts in the DUR field have raised serious questions

about the ability of the point-of-sale system envisioned by The Health Care Financing Administration to accomplish prospective DUR. Besides questions about its feasibility, prospective DUR raises additional concerns about safeguarding patient confidentiality and avoiding unnecessary interference in the patient/physician and patient/pharmacist relationships.

4. PMA believes that, given the lack of experience of applying DUR to an outpatient drug program with over 700 million claims, it is essential that deliberations and ultimate decisions on Medicare DUR be open to input and debate by the public and scientific community.

Labeling of Medications for the Elderly

FDA approved labeling for drugs given market approval in recent years does contain specific information on the elderly.

To enhance the value of label information for physicians and patients, the industry would be pleased to work with FDA to improve the Dosage and Administration part of the product label as it pertains to the elderly.

In my experience, the "Dosage and Administration" part of the label is the part most heavily consulted by practitioners.

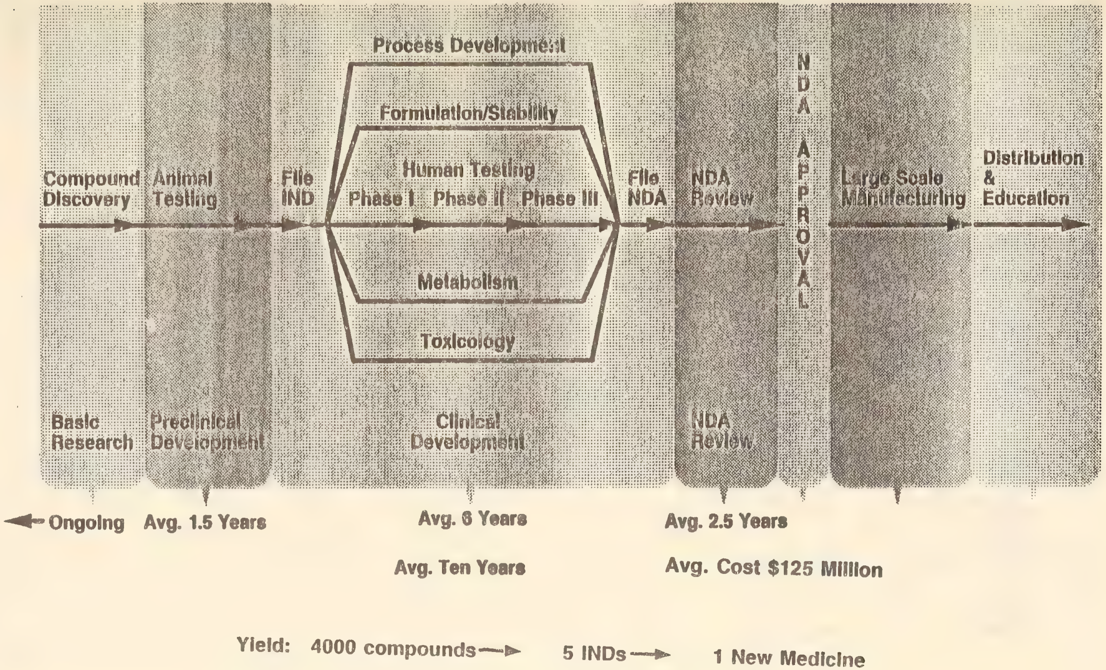
Conclusion

In conclusion, aging often brings with it a complex set of health problems for both patient and physician. As our older population continues to increase, so will the incidence of diseases prevalent among this age group, such as cardiovascular disease, many cancers and debilitating diseases like Alzheimer's and arthritis.

Many of these health problems are best treated by prescription drugs--they can keep people out of hospitals, reduce the need for costly surgeries and allow older citizens to remain independent and productive longer. But along with the benefits of today's great variety of medicines comes the need to ensure that older patients use medicines properly. We will do our part by working with you and the medical profession to advance the health care of the elderly.

Attachments:		
	Figure 1	Drug Development Process
	Appendix 1	New Medicines for Elderly - 3 charts
	Appendix 2	Drug Development Process
	Appendix 3	1988 Drug Approvals chart

Drug Development Process



IN DEVELOPMENT
NEW MEDICINES
FOR OLDER AMERICANS

Presented by the Pharmaceutical Manufacturers Association

October 1988

No. 1 Target of Research

Survey Finds 87 Drugs in Development for Cardiovascular Disease

Cardiovascular disease, the leading cause of death among older persons, has become the number one target for new drug research and development by the U.S. pharmaceutical industry.

A new survey by the Pharmaceutical Manufacturers Association shows 47 companies are developing 87 drugs for heart disease, hypertension and stroke, more than are being tested for any other disease.

Pharmaceutical companies spend the largest portion of their research and development investment—nearly 26 percent—on finding medicines for heart and circulatory disease, accounting for approximately $1.4 billion of the industry's $5.4 billion research and development budget in 1987.

The PMA survey of heart disease drugs in development is part of a series of surveys, "New Medicines for Older Americans," conducted by the association. The results show products in the industry's research pipeline that are targeted for diseases that primarily afflict older persons.

Details of the drugs in development for other aging diseases will be released by the PMA over a 4-month period in a series of charts.

All the drugs in this first chart in the series—Heart/Stroke/ Hypertension—are in human test stages or awaiting approval at the Food and Drug Administration.

30 of the 87 products are being tested for more than one indication, or use, resulting in 123 separate research and development projects. These are listed separately in the attached chart.

The most concentrated testing and development is for hypertension. Some 38 products are being tested for this use; all but 3 of them are in the final stages of development.

Heart Disease
Stroke
Hypertension
First of a series
on
New Medicines
for Older Americans.

Many products being tested for other cardiovascular diseases also are tested for hypertension because of its close association with other heart diseases. According to the Public Health Service, controlling high blood pressure can be one of the most effective means available of saving lives because hypertension can lead to heart disease and stroke.

The second most concentrated area of testing is congestive heart failure, the final and potentially fatal result of heart and vascular disease problems. There are 28 products in development for congestive heart failure, two-thirds of which are in advanced development stages.

There are 8 products in tests for arrhythmia, 9 for atherosclerosis, 17 for coronary artery disease/angina, 7 for heart attack and 8 for peripheral vascular disease.

Of the 6 products for stroke, 3 are versions of tissue plasminogen activator (tPA), which already is approved for treatment of heart attacks.

Heart disease is the leading cause of death in the United States, particularly among older persons, and stroke ranks third. Some 36 percent of all U.S. deaths are the result of heart disease and 7 percent are the result of stroke.

Although the death rate from cardiovascular disease has dropped 41 percent in the past 20 years from 363 to 213 per 100,000 population, the aging of the population is likely to result in increased incidence of cardiovascular disease.

I am pleased to release this list of the 87 new drug therapies that are being developed for heart and circulatory diseases by the nation's pharmaceutical industry.

New medicines for older Americans hold the promise of longer, better quality lives and also can result in shorter hospital stays, fewer operations, and continued independence for older persons. With the increasing numbers of older persons in our society, this clearly is one of our industry's most important challenges.

Gerald J. Mossinghoff, *President*
Pharmaceutical Manufacturers
Association

Cardiovascular Products In Development

Arrhythmia

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
CK 1752 Sematilide	Berlex Laboratories (Wayne, NJ)		Phase II
Diprafenone	Berlex Laboratories (Wayne, NJ)		Phase II
Lopressor Metoprolol Tartrate	Ciba-Geigy (Summit, NJ)	(See also coronary artery disease/angina)	application submitted
Decabid Indecanide	Eli Lilly (Indianapolis, IN)		in human clinicals
Cipralan Cifenline	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)		application submitted
Rythmol Propafenone	Knoll Pharmaceuticals (Whippany, NJ)		application submitted
Recainam	Wyeth-Ayerst (Radnor, PA)		Phase III
WY-48,986	Wyeth-Ayerst (Radnor, PA)		Phase I

Atherosclerosis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
BMY 21891	Bristol-Myers (New York, NY)	(See also coronary artery disease)	Phase I
HWA 448 Torbafylline	Hoechst-Roussel (Somerville, NJ)	(See also peripheral vascular disease)	Phase II
15-Ketosterol	Lederle (Wayne, NJ)		Phase I
Nilvadipine (calcium channel blocker)	Lederle (Wayne, NJ)	(See also hypertension)	in human clinicals
TA 3090	Marion Laboratories (Kansas City, MO)	(See also coronary artery disease/angina, hypertension, peripheral vascular disease)	Phase I
DynaCirc Isradipine	Sandoz (East Hanover, NJ)	(See also hypertension)	Phase III
Pravachol Pravastatin	Squibb (Princeton, NJ)		application submitted
Cardene Nicardipine	Syntex (Palo Alto, CA)	(See also coronary artery disease/angina, hypertension, stroke)	Phase II
Ciprostene Calcium	Upjohn (Kalamazoo, MI)	(adjunct therapy for balloon angioplasty; see also peripheral vascular disease)	Phase II

Congestive Heart Failure

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Manoplax Flosequinan, BTS 49,465	The Boots Company (Lincolnshire, IL)	(See also hypertension)	Phase III

The content of this chart has been obtained through industry sources based on the latest information. Chart current as of October 15, 1988. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. For general information, contact the Pharmaceutical Manufacturers Association at (202) 835-3463. *(If you did not receive your own copy of this issue of "New Medicines for Older Americans," please write to the Communications Division at the Pharmaceutical Manufacturers Association.)*

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Peripheral Vascular Disease

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Abbokinase Urokinase	Abbott Labs (North Chicago, IL)	(See also coronary artery disease/angina)	application submitted
Mg EDTA	A.H. Robins (Richmond, VA)		Phase II
Iloprost	Berlex Laboratories (Wayne, NJ)		Phase II
HWA 448 Torbafylline	Hoechst-Roussel (Somerville, NJ)	(See also atherosclerosis)	Phase II
Sufrexal/ Ketanserin	Janssen Pharmaceutica (Piscataway, NJ)	(See also hypertension)	Phase II/III
TA 3090	Marion Laboratories (Kansas City, MO)	(See also atherosclerosis, coronary artery disease/angina, hypertension)	Phase I
Ciprostene Calcium	Upjohn (Kalamazoo, MI)	(See also atherosclerosis)	Phase II
Itazigrel	Upjohn (Kalamazoo, MI)		Phase II

Stroke (Cerebral Thrombosis)

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Prolysis (+PA)	Burroughs Wellcome (Research Triangle Park, NC)	(See also heart attack)	application submitted
Tissue Plasminogen Activator	Genetics Institute (Cambridge, MA) Wellcome Biotechnology (Beckenham, England)	(See also heart attack, other)	Phase II/III
Arvin Ancrod	Knoll Pharmaceuticals (Whippany, NJ)		Phase II
ORG 10172	Organon (West Orange, NJ)		Phase II
Cardene Nicardipine	Syntex (Palo Alto, CA)	(See also atherosclerosis, coronary artery disease/angina, hypertension)	Phase II
Ticlid Ticlopidine	Syntex (Palo Alto, CA)		Phase III

Other

DRUG	COMPANY	INDICATIONS	U.S. DEVELOPMENT STATUS
Digidote Digoxin Immune Fab-Ovine	Boehringer Mannheim (Rockville, MD)	life-threatening acute cardiac glycoside intoxication	application submitted
Tissue Plasminogen Activator	Genetics Institute (Cambridge, MA) Wellcome Biotechnology (Beckenham, England)	pulmonary embolism (See also heart attack, stroke)	application pending

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Congestive Heart Failure

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
RS 93522	Syntex (Palo Alto, CA)	(See also hypertension)	Phase I
Nicorandil	Upjohn (Kalamazoo, MI)	(See also coronary artery disease/angina)	Phase II
CI-906 Quinapril Accupril	Warner-Lambert (Morris Plains, NJ)	(See also hypertension)	Phase III
Anaritide Peptide with Vasomotor Activity	Wyeth-Ayerst (Radnor, PA)		Phase II

Coronary Artery Disease/Angina

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Abbokinase Urokinase	Abbott Labs (North Chicago, IL)	(See also peripheral vascular disease)	Phase II
Procardia® XL Nifedipine	Alza (Palo Alto, CA) Pfizer (New York, NY)	(For angina only; see also hypertension)	application submitted
Eminase	Beecham Laboratories (Bristol, TN)		application submitted
Carvedilol SKF-105517	Boehringer Mannheim (Rockville, MD) SmithKline Beckman (Philadelphia, PA)	(For angina only; see also hypertension)	Phase III
BMY 21891	Bristol-Myers (New York, NY)	(See also atherosclerosis)	Phase I
Lopressor Metoprolol Tartrate	Ciba-Geigy (Summit, NJ)	(See also arrhythmia)	application submitted
Bisoprolol Fumarate	Lederle (Wayne, NJ)	(For angina only; see also hypertension)	Phase III
TA 3090	Marion Laboratories (Kansas City, MO)	(See also atherosclerosis, hypertension, peripheral vascular disease)	Phase I
McN-5691	McNeil Pharmaceutical (Spring House, PA)	(For angina only; see also hypertension)	Phase II
Vascor® Bepridil	McNeil Pharmaceutical (Spring House, PA)		application submitted
Plendil MK-218/ Felodipine	Merck Sharp & Dohme (West Point, PA) Astra Pharmaceutical (Westboro, MA)	(For angina only; see also congestive heart failure, hypertension)	Phase III
Amlodipine	Pfizer (New York, NY)	(For angina only; see also hypertension)	application submitted
Sulotroban SK & F 95587	SmithKline Beckman (Philadelphia, PA)		Phase II
Cardene Nicardipine	Syntex (Palo Alto, CA)	(For angina only; see also atherosclerosis, hypertension, stroke)	Phase II
RS 43285	Syntex (Palo Alto, CA)	(For angina only)	Phase II
Nicorandil	Upjohn (Kalamazoo, MI)	(For angina only; see also congestive heart failure)	Phase II
Betridil	Wallace Laboratories (Cranbury, NJ) McNeil Pharmaceutical (Spring House, PA)	(For angina only)	Phase III

Heart Attack (Coronary Thrombosis; Myocardial Infarction)

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Tissue Plasminogen Activator	Biogen (Cambridge, MA) SmithKline Beckman (Philadelphia, PA)		Phase II
Superoxide Dismutase	Bio-technology General (New York, NY)		Phase II
BM-13.177 SKF-95587	Boehringer Mannheim (Rockville, MD) SmithKline Beckman (Philadelphia, PA)		Phase II
Prolysis (+PA)	Burroughs Wellcome (Research Triangle Park, NC)	(See also stroke)	application submitted
Centorex Anti-platelet MAb	Centocor (Malvern, PA)		Phase I
Prourokinase	Collaborative Research (Bedford, MA) Sandoz (East Hanover, NJ)		Phase II/III
Tissue Plasminogen Activator	Genetics Institute (Cambridge, MA) Wellcome Biotechnology (Beckenham, England)	(See also stroke, other)	Phase II/III

Hypertension

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Hytrin/Enduron Terazosin/ Methyclothiazide combination	Abbott Labs (North Chicago, IL)		Phase III
Bopindolol	A.H. Robins (Richmond, VA)		Phase III
Quanfacine	A.H. Robins (Richmond, VA)		Phase III
Minipress/ Prazosin XL	Alza (Palo Alto, CA) Pfizer (New York, NY)		application submitted
OROS Potassium Chloride for Potassium Supplementation	Alza (Palo Alto, CA)		application submitted
Procardia® XL Nifedipine	Alza (Palo Alto, CA) Pfizer (New York, NY)	(See also coronary artery disease/angina)	application submitted
Carvedilol SKF-105517	Boehringer Mannheim (Rockville, MD) SmithKline Beckman (Philadelphia, PA)	(See also coronary artery disease/angina)	Phase III

Hypertension

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Manoplax Flosequinan, BTS 49,465	The Boots Company (Lincolnshire, IL)	(See also congestive heart failure)	Phase III
Benazepril	Ciba-Geigy (Summit, NJ)	(See also congestive heart failure)	application submitted
Pindac Pinacidil	Eli Lilly (Indianapolis, IN)		application submitted
Kerlone	G.D. Searle and Company (Chicago, IL)		application submitted
Cardace® Ramipril	Hoechst-Roussel (Somerville, NJ)	(See also congestive heart failure)	Phase III
Symcor Tiamenidine HCl	Hoechst-Roussel (Somerville, NJ)		application submitted
Baypress Nitrendipine	Hoffmann-La Roche (Nutley, NJ) Miles Inc. (West Haven, CT)		application submitted
Inhibace Cilazapril	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)	(See also congestive heart failure)	Phase III
Inhibace Cilazapril/HCTZ	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)		Phase III
Sufrexal/ Ketanserin	Janssen Pharmaceutica (Piscataway, NJ)	(See also peripheral vascular disease)	Phase II/III
Bisoprolol Fumarate	Lederle (Wayne, NJ)	(See also coronary artery disease/angina)	Phase III
Nilvadipine (calcium channel blocker)	Lederle (Wayne, NJ)	(See also atherosclerosis)	in human clinicals
Cardizem SR Diltiazem HCl Sustained Release	Marion Laboratories (Kansas City, MO)		application submitted
TA 3090	Marion Laboratories (Kansas City, MO)	(See also atherosclerosis, coronary artery disease/angina, peripheral vascular disease)	Phase I
McN-5691	McNeil Pharmaceutical (Spring House, PA)	(See also coronary artery disease/angina)	Phase II
Perindopril	McNeil Pharmaceutical (Spring House, PA)	(See also congestive heart failure)	Phase III
Plendil MK-218/ Felodipine	Merck Sharp & Dohme (West Point, PA) Astra Pharmaceutical (Westboro, MA)	(See also congestive heart failure, coronary artery disease/angina)	Phase III
Amlodipine	Pfizer (New York, NY)	(See also coronary artery disease/angina)	application submitted
Cardura Doxazosin	Pfizer (New York, NY)		application submitted
Celectol Celiprolol	Rorer Group (Fort Washington, PA)	(See also congestive heart failure)	application submitted

Congestive Heart Failure

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Bucindolol	Bristol-Myers (New York, NY)		Phase II
Auriculin Atrial Peptide	California Biotechnology (Mountain View, CA) Wyeth-Ayerst (Radnor, PA)		Phase II
Benazepril	Ciba-Geigy (Summit, NJ)	(See also hypertension)	Phase III
Indolidan	Eli Lilly (Indianapolis, IN)		in human clinicals
Isomazole	Eli Lilly (Indianapolis, IN)		in human clinicals
Dopacard Dopexamine Hydrochloride Solution	Fisons Corporation (Bedford, MA)		Phase III
Arlix Piretanide	Hoechst-Roussel (Somerville, NJ)	(Also for edema)	application submitted
Cardace® Ramipril	Hoechst-Roussel (Somerville, NJ)	(See also hypertension)	Phase III
Inhibace Cilazapril	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)	(See also hypertension)	Phase III
Carwin Xamoterol	ICI Pharmaceuticals (Wilmington, DE)		Phase III
ICI 153-110	ICI Pharmaceuticals (Wilmington, DE)		Phase I
Perindopril	McNeil Pharmaceutical (Spring House, PA)	(See also hypertension)	Phase III
Plendil MK-218/ Felodipine	Merck Sharp & Dohme (West Point, PA) Astra Pharmaceutical (Westboro, MA)	(See also coronary artery disease/angina, hypertension)	Phase III
Perfan Enoximone	Merrell Dow (Cincinnati, OH)		Phase III
Piroximone MDL 19,205	Merrell Dow (Cincinnati, OH)		Phase II
ORF-22867	Ortho Pharmaceutical (Raritan, NJ)		Phase I
Celectol Celiprolol	Rorer Group (Fort Washington, PA)	(See also hypertension)	application submitted
RGW-2938	Rorer Group (Fort Washington, PA)		Phase II
Spirapril	Schering-Plough (Madison, NJ) Sandoz (East Hanover, NJ)	(See also hypertension)	Phase III
Corlopam Fenoldopam— SK & F 82526	SmithKline Beckman (Philadelphia, PA)	(See also hypertension)	Phase III
Zofenopril	Squibb (Princeton, NJ)	(See also hypertension)	Phase III
Medorinone	Sterling Drug (New York, NY)		Phase I
Milrinone	Sterling Drug (New York, NY)		Phase III

Hypertension

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
DynaCirc Isradipine	Sandoz (East Hanover, NJ)	(See also atherosclerosis)	application submitted
Spirapril	Schering-Plough (Madison, NJ) Sandoz (East Hanover, PA)	(See also congestive heart failure)	Phase III
Unicard® Dilevalol	Schering-Plough (Madison, NJ)		application submitted
Carvedilol SK & F 105517	SmithKline Beckman (Philadelphia, PA)		Phase III
Corlopam Fenoldopam— SK & F 82526	SmithKline Beckman (Philadelphia, PA)	(See also congestive heart failure)	Phase III
Fosinopril	Squibb (Princeton, NJ)		Phase III completed
Zofenopril	Squibb (Princeton, NJ)	(See also congestive heart failure)	Phase III
Cardene Nicardipine	Syntex (Palo Alto, CA)	(See also atherosclerosis, coronary artery disease/angina, stroke)	application submitted
RS 93522	Syntex (Palo Alto, CA)	(See also congestive heart failure)	Phase I
CI-775 Bevantolol	Warner-Lambert (Morris Plains, NJ)		application submitted
CI-906 Quinapril Accupril	Warner-Lambert (Morris Plains, NJ)	(See also congestive heart failure)	Phase III

GLOSSARY

Adjunct—A substance or drug that aids or helps another drug to act.

Angina (pectoris)—A symptom of coronary artery disease. Narrowed coronary arteries result in decreased blood flow to the heart muscle typically causing chest pain in the area of the heart.

Application submitted—An application for marketing has been submitted by the company to the Food and Drug Administration (FDA).

Arrhythmia—Abnormal heart rhythm usually detected by an electrocardiogram. Arrhythmias can be caused by several factors, such as coronary artery disease, heart valve problems or hyperthyroidism.

Atherosclerosis—A common disease in which deposits of plaque containing fatty substances, like cholesterol, are formed within the inner layer of the arteries. A common name for it is "hardening of the arteries." Atherosclerosis is a progressive condition over decades, chiefly affecting the arteries of the heart, brain and extremities. Its complications, such as coronary artery disease and strokes, are the major causes of death in the United States.

Balloon angioplasty—A balloon catheter is inserted into a clogged or narrowed coronary artery to improve blood circulation by dilating the vessel, either by flattening plaque against the artery wall or by breaking up the plaque.

Cardiac glycoside intoxication—Cardiac glycoside is a drug that helps a failing heart to pump more strongly. Although cardiac glycosides, such as digoxin, are sometimes used in treating congestive heart failure, there is a fine line between their therapeutic and toxic levels. Too much digoxin, for instance, can cause anorexia, nausea and vomiting, headache, vision problems and disorientation. All of these symptoms can precede serious cardiac toxicity, which most often manifests itself as arrhythmias.

Congestive heart failure (CHF)—In CHF, the end result of many different types of heart disease, the heart cannot pump blood out normally. This results in congestion (water and salt retention) in the lungs, edema in the extremities and reduced blood flow to body tissues.

Coronary artery disease (CAD)—Atherosclerosis of the large and medium-sized arteries of the heart is the cause of most CAD. The major complications of CAD are angina pectoris, heart attacks and congestive heart failure. It is the most common cause of cardiovascular disability and death in the United States.

Edema—Abnormally large amounts of fluid build up in body tissues causing swelling.

Heart attack/coronary thrombosis/myocardial infarction—A coronary thrombosis is a blood clot in an artery of the heart that obstructs the blood flow and can cause sudden death. In myocardial infarction, a part of the heart muscle (myocardium) dies as a result of blood and oxygen deprivation.

Hypertension—More than 60 million adults in the United States have hypertension, also known as high blood pressure. Without treatment, it greatly increases the incidence of cardiovascular disease—coronary artery disease, heart attack, stroke and kidney failure. In about 95 percent of the cases, there is no known cause.

Peripheral vascular disease—The obstruction of blood supply to the extremities, particularly the legs, caused by atherosclerosis.

Phase I—Safety testing and pharmacological profiling in humans.

Phase II—Effectiveness testing in humans.

Phase III—Extensive clinical trials in humans.

Pulmonary embolism—A blood clot that obstructs the pulmonary artery, which transports blood from the heart to the lungs. More than 90 percent of pulmonary emboli originate as clots in the deep veins of the lower extremities. In some cases, they result in sudden death.

Stroke/cerebral thrombosis—Usually caused by atherosclerosis, a blood clot obstructs a major blood vessel of the brain, resulting in death or serious brain damage, such as paralysis or loss of speech.

Provided as a Public Service by the Pharmaceutical Manufacturers Association.

IN DEVELOPMENT
NEW MEDICINES
FOR OLDER AMERICANS

Presented by the Pharmaceutical Manufacturers Association
In cooperation with the American Cancer Society

December 1988

65 Drugs in Development

Anti-Cancer Research Gaining Momentum, Survey Shows

Sixty-five cancer drugs that are now in development are targeted to treat cancers commonly associated with older persons—including breast, colon, lung, mouth, prostate and skin cancers.

These 65 medicines are being developed by 45 companies.

The figures indicate that a strong anti-cancer research and development effort is underway by the nation's pharmaceutical companies— an effort that is significantly enhanced by biotechnology research techniques.

At least 19 of these medicines—29 percent—are biotechnology-based drugs. Biotechnology has become important to anti-cancer research because it helps explain how cancers develop in the body and enables researchers to boost the body's immune system to fight cancers. An earlier PMA survey of biotechnology medicines in development found that approximately 50 percent—48 drugs—were targeted against cancers that afflict all ages.

It seems clear that anti-cancer research is gathering momentum, although I must stress that the therapeutic significance of these medicines will not be known until clinical studies are completed and evaluated.

PMA joins the American Cancer Society in hoping that this listing of drugs in clinical trials will encourage more patients to volunteer for these trials.

This cancer drug survey is part of a broader PMA effort to identify all the products that are being developed to treat the principal diseases of older Americans. We are attempting in these surveys to quantify the extensive private sector research against such diseases.

The first survey in our "New Medicines for Older Americans' series identified 87 drugs that are being developed by 47 companies for heart disease, stroke and hypertension.

Cancer

Second of a series
on
New Medicines
for Older Americans.

Cancer is second only to cardiovascular disease as the leading cause of death in older people. The American Cancer Society estimates that 985,000 Americans will be diagnosed as having cancer in 1988, and more than half of them will be over age 65. Nearly 60 percent of the 395,000 Americans who will die from cancer this year will be over age 65.

Among the findings in the survey:

- 14 of the 65 products are being tested for more than one indication, or use, resulting in 97 separate clinical test projects, each of which is listed in the chart.
- 25 products being tested are for unspecified forms of cancer (listed under "Other" in the chart).
- 20 drugs are being tested for colon cancer, which will strike an estimated 105,000 persons this year and prove fatal for 53,500; 94 percent of those diagnosed with colorectal cancer will be over age 50.
- 16 drugs are targeted to treat breast cancer. About 135,000 new cases of breast cancer will be diagnosed this year, and 42,000 women will die of the disease. Since 1950, the rate of death caused by breast cancer for women age 50 and older has been consistently increasing.
- 14 are intended to treat lung cancer. Lung cancer is the most common form of cancer in the United States and the leading cause of cancer deaths. The incidence of lung cancer sharply increases after age 55. There will be an estimated 152,000 new cases in the United States in 1988 and approximately 139,000 deaths.
- 10 medicines are in tests or awaiting approval for prostate cancer, with an estimated 99,000 new cases and 28,000 deaths in 1988. About 80 percent of prostate cancers are diagnosed in men over 65 years old.
- 11 drugs also are in tests or awaiting approval to treat skin cancers, including the most serious type, malignant melanoma, which occurs in about 27,000 people annually and causes 5,800 deaths.
- 1 product is intended to treat mouth (oral cavity) cancer, which will be diagnosed in about 30,000 people this year, killing 9,100.

The final survey in our series of "New Medicines for Older Americans" will identify medicines in development for arthritis, Alzheimer's and other diseases. This is scheduled for completion January 31.

Gerald J. Mossinghoff, *President*
Pharmaceutical Manufacturers Association

Cancer Products In Development

Breast Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Epirubicin	Adria (Columbus, OH)		application submitted
Toremifene	Adria (Columbus, OH)		Phase II/III
Elobromol Dibromodulcitol	Amswiss Pharmaceuticals, Inc. (San Antonio, TX)	(See also lung, skin)	Phase II
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also colon, lung, prostate)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also colon, lung, prostate)	Phase I/II
L-6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also colon, lung, prostate)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also colon, lung, prostate)	Phase II/III
Proleukin Interleukin–2	Cetus (Emeryville, CA)	(See also colon, lung, skin)	Phase II
A.P.D. CGS 16949	Ciba-Geigy (Summit, NJ)		Phase III
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also colon, lung, prostate)	in clinical trials
LY188011 Difluorodeoxycytidine	Eli Lilly (Indianapolis, IN)	(See also colon, lung)	in clinical trials
LY264618	Eli Lilly (Indianapolis, IN)	(See also colon, lung)	in clinical trials
Fenretinide	McNeil Pharmaceutical (Spring House, PA)		Phase III
MDL 18,962	Merrell Dow (Cincinnati, OH)		Phase I
Tomosar SP Menogaril	Upjohn (Kalamazoo, MI)		Phase II
Liposomal Doxirubicin	Vestar (San Dimas, CA) Lyphomed, Inc. (Rosemont, IL)		Phase II

Colon Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also breast, lung, prostate)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also breast, lung, prostate)	Phase I/II
L–6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also breast, lung, prostate)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also breast, lung, prostate)	Phase II/III
Panorex MAb 17–1A	Centocor (Malvern, PA)		Phase II
Proleukin Interleukin–2	Cetus (Emeryville, CA)	(See also breast, lung, skin)	Phase II
CYT–103^{90}Y	CYTOGEN Corp. (Princeton, NJ)		Phase I

The content of this chart has been obtained through industry sources based on the latest information. Chart current as of December 1, 1988. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. For general information, contact the Pharmaceutical Manufacturers Association at (202) 835-3463. *(If you did not receive your own copy of this issue of "Cancer Products in Development," please write to the Communications Division at the Pharmaceutical Manufacturers Association.)*

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Skin Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Roferon®–A Interferon alfa-2a	Hoffmann-La Roche (Nutley, NJ)		Phase II
RETIN–A® Tretinoin	Ortho Pharmaceutical (Raritan, NJ)		Phase III
Detox™	Ribi ImmunoChem Research (Hamilton, MT)		Phase II
Intron A Interferon-alpha2b	Schering-Plough (Madison, NJ)		application submitted
XomaZyme®–Mel	Xoma (Berkeley, CA)	(See also colon)	Phase II

Other

(drugs that have potential for one or more of the previous cancers; indications not yet determined)

DRUG	COMPANY	INDICATIONS	U.S. DEVELOPMENT STATUS
BMY–25801	Bristol-Myers (New York, NY)	adjunct to chemotherapy	Phase II/III
BMY–28175	Bristol-Myers (New York, NY)		Phase I
Alkeran	Burroughs Wellcome (Research Triangle Park, NC)		Phase III
Piritrexim	Burroughs Wellcome (Research Triangle Park, NC)		Phase II
DuP–785	Du Pont (Wilmington, DE)		Phase II
Radinyl® Etanidazole	Du Pont (Wilmington, DE) Roberts (Eatontown, NJ)	(See also lung, mouth)	Phase II/III
Tumor Necrosis Factor (TNF)	Genentech (S. San Francisco, CA)		Phase II
Macrophage Colony Stimulating Factor (M-CSF)	Genetics Institute (Cambridge, MA)	(See also colon, skin)	Phase I
Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)	Immunex (Seattle, WA) Behringwerke A.G. (subsidiary of Hoechst A.G. Marburg, W. Germany)		Phase II/III
Amonafide	Knoll Pharmaceuticals (Whippany, NJ)		Phase I
Tumor Necrosis Factor (TNF)	Knoll Pharmaceuticals (Whippany, NJ)		Phase I
Fazarabine	Lederle (Wayne, NJ)		Phase II
Platinum I	Lederle (Wayne, NJ)		Phase I
Platinum II	Lederle (Wayne, NJ)		Phase I
DOX 99 Doxorubicin Liposomal	The Liposome Company (Princeton, NJ)		Phase I
Plat 23	The Liposome Company (Princeton, NJ)		Phase I
Interleukin–2	Ortho Pharmaceutical (Raritan, NJ) Amgen (Thousand Oaks, CA)		in clinical trials
Decapeptyl™	Organon, Inc. (West Orange, NJ)	(See also prostate)	Phase II

Lung Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
LY264618	Eli Lilly (Indianapolis, IN)	(See also breast, colon)	in clinical trials
Radinyl® Etanidazole	Du Pont (Wilmington, DE) Roberts (Eatontown, NJ)	(See also mouth, other)	Phase II/III
CI–898 Trimetrexate	Warner-Lambert (Morris Plains, NJ)		Phase III

Mouth (oral cavity) Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Radinyl® Etanidazole	Du Pont (Wilmington, DE) Roberts (Eatontown, NJ)	(See also lung, other)	Phase II/III

Prostate Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also breast, colon, lung)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also breast, colon, lung)	Phase I/II
L–6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also breast, colon, lung)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also breast, colon, lung)	Phase II/III
Suprefact® Buserelin	Hoechst-Roussel (Somerville, NJ)		application submitted
Zoladex Goserelin Acetate	ICI Pharmaceuticals (Wilmington, DE)		application submitted
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also breast, colon, lung)	in clinical trials
Decapeptyl™	Organon, Inc. (West Orange, NJ)	(See also other)	Phase III
Eulexin® Flutamide	Schering-Plough (Madison, NJ)		application submitted
Lupron Leuprolide Acetate	TAP Pharmaceuticals (N. Chicago, IL)	for monthly injection	application submitted

Skin Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Elobromol Dibromodulcitol	Amswiss Pharmaceuticals, Inc. (San Antonio, TX)	(See also breast, lung)	Phase II
Proleukin Interleukin–2	Cetus (Emeryville, CA)	(See also breast, colon, lung)	Phase III
Actinex	Chemex (Denver, CO)		Phase II
Gamma Interferon	Genentech (S. San Francisco, CA)	(See also colon, lung)	Phase III
Macrophage Colony Stimulating Factor (M-CSF)	Genetics Institute (Cambridge, MA)	(See also colon, other)	Phase I
IL–2 Interleukin–2	Hoffmann-La Roche (Nutley, NJ)		Phase II/III
	Immunex (Seattle, WA)	in combination w/**Roferon® –A**	Phase II

Colon Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Gamma Interferon	Genentech (S. San Francisco, CA)	(See also lung, skin)	Phase III
Macrophage Colony Stimulating Factor (M-CSF)	Genetics Institute (Cambridge, MA)	(See also skin, other)	Phase I
Monoclonal Antibody (NRCO–4)	Genetics Institute (Cambridge, MA) NeoRx (Seattle, WA)		Phase I
Leucovorin Calcium (w/5-fluorouracil)	Lederle (Wayne, NJ)		application submitted
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also breast, lung, prostate)	in clinical trials
LY188011 Difluorodeoxycytidine	Eli Lilly (Indianapolis, IN)	(See also breast, lung)	in clinical trials
LY264618	Eli Lilly (Indianapolis, IN)	(See also breast, lung)	in clinical trials
MDL 72,175	Merrell Dow (Cincinnati, OH)		Phase I
Colon RE–186	NeoRx (Seattle, WA)		Phase I
Tauricyt Tauromustine (TCNU)	Pharmacia (Piscataway, NJ)		Phase III
Ovamid™	Ribi ImmunoChem Research (Hamilton, MT)		Phase I
Spiro 32 Spirogermanium	Unimed (Somerville, NJ)		Phase II
XomaZyme®–Mel	Xoma (Berkeley, CA)	(See also skin)	Phase I

Lung Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Neupogen™ Granulocyte Colony Stimulating Factor	Amgen (Thousand Oaks, CA)	adjunct to enhance effect of chemotherapy	Phase III
Elobromol Dibromodulcitol	Amswiss Pharmaceuticals, Inc. (San Antonio, TX)	(See also breast, skin)	Phase II
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also breast, colon, prostate)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also breast, colon, prostate)	Phase I/II
L–6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also breast, colon, prostate)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also breast, colon, prostate)	Phase II/III
Interleukin–2 with Tumor Necrosis Factor (TNF)	Cetus (Emeryville, CA)		Phase I/II
Proleukin Interleukin–2	Cetus (Emeryville, CA)	(See also breast, colon, skin)	Phase II
Gamma Interferon	Genentech (S. San Francisco, CA)	(See also colon, skin)	Phase III
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also breast, colon, prostate)	in clinical trials
LY188011 Difluorodeoxycytidine	Eli Lilly (Indianapolis, IN)	(See also breast, colon)	in clinical trials

Other *(drugs that have potential for one or more of the previous cancers; indications not yet determined)*

DRUG	COMPANY	INDICATIONS	U.S. DEVELOPMENT STATUS
Sterecyt Prednimustine	Pharmacia (Piscataway, NJ)		Phase II
Speratine™ Spiromustine	Roberts (Eatontown, NJ)		Phase II
Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)	Schering-Plough (Madison, NJ) Sandoz (East Hanover, NJ) Genetics Institute (Cambridge, MA)	adjuvant to chemotherapy	Phase II/III
Carbetimer	G.D. Searle & Co. (Chicago, IL)		Phase II
Interleukin–4	Sterling Drug (New York, NY) Immunology Ventures (Seattle, WA)		Phase I
Liposomal Daunorubicin	Vestar (San Dimas, CA)		Phase I
AS101	Wyeth-Ayerst (Philadelphia, PA)		Phase II

GLOSSARY

Adjuvant/adjunct—A substance or drug that aids or helps another become effective or more effective. An adjunct also aids the delivery of a drug to a place where it is most effective in the body.

Application submitted—An application for marketing has been submitted by the company to the Food and Drug Administration (FDA).

Phase I—Safety testing and pharmacological profiling in humans.
Phase II—Effectiveness testing in humans.
Phase III—Extensive clinical trials in humans.

A Strong System is Needed to Recruit Participants for Clinical Testing of Cancer Drugs

by Gerald P. Murphy, M.D., Senior Vice President, Medical Affairs, American Cancer Society

This chart from the Pharmaceutical Manufacturers Association of anti-cancer drugs in clinical trials can help in at least two ways with a very tough problem—obtaining enough participants for cancer drug clinical trials.

1. *Doctors and patients are not sufficiently aware of what drugs are available and where they are being tested.* Information is the first step in getting people into advanced treatment programs. We have that information now in a readily accessible form.

This chart contains comprehensive information on cancer drugs in the clinical test phase, and the American Cancer Society will assist in getting it to oncologists and their patients.

2. *Some patients avoid clinical trials, because they are under the erroneous impression that the patient may end up in a control group and get a placebo instead of the experimental medicine.* Clearly, the patients and their physicians must thoroughly satisfy themselves concerning study design, but the fact is, current practice in cancer research involves the use of standard treatment as the control. That is, the new treatment is compared to the existing standard treatment, if there is one. The American Cancer Society advises that such trials be viewed as being consistent with the best medical care that an individual with cancer can receive.

We are confident that this chart, with its valuable information about drugs in development and their sources, can lead to greater trial participation by making it easier for physicians to inquire about the trials and by satisfying concerns about control group treatment.

It is apparent from the chart that research-based pharmaceutical companies are engaged in an enormous effort to develop promising new therapies for cancer. This list presents only a partial picture of therapies in development—only those that have progressed to clinical trial stage. Yet it is clear that the outlook for drug therapy has never been more promising.

The eventual delivery of these drugs from the laboratory to the patient depends greatly on the clinical test system to satisfy questions of safety and efficacy. This system cannot be permitted, through inadequate available participants, to become the weak link in speeding these drugs into widespread use.

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IN DEVELOPMENT
NEW MEDICINES
FOR OLDER AMERICANS

Presented by the Pharmaceutical Manufacturers Association
In cooperation with
Alliance for Aging Research, American Diabetes Association, Arthritis Foundation, and National Council on the Aging

January 1989

Research on Aging Increases

69 New Drugs in Testing for 9 Debilitating Diseases

America's research-based pharmaceutical companies are developing 69 new drugs intended to treat 9 diseases that often cripple and disable older persons. These drugs are being developed by 48 companies.

Ten of the 69 drugs are being tested for more than one indication, or use, resulting in 81 separate research and development projects. These are listed separately in the attached chart.

Three diseases that are leading causes of nursing home admissions are targets for more than half of the 81 research projects identified in this PMA survey:

- 25 drugs are in development for arthritis (15 for rheumatoid arthritis and 10 for osteoarthritis),
- 15 for Alzheimer's disease, and
- 10 for osteoporosis.

Effective treatments for these three debilitating diseases will not only make life more livable in later years, but reduce the costs associated with long term care.

Also in development for diseases that primarily affect older persons are:

- 16 drugs for depression,
- 6 for Parkinson's disease,
- 4 for adult onset diabetes,
- 3 for glaucoma, and
- 2 for gout.

Adult Onset Diabetes

Alzheimer's Disease

Arthritis

Third of a series on New Medicines for Older Americans.

These findings are the latest in the PMA "New Medicines for Older Americans" series that seeks to identify all medicines that have reached the human test stage for diseases that have a major impact on older persons.

Earlier surveys identified 87 drugs for heart disease, stroke and hypertension, and 65 for cancers common to older people. The 221 medicines in development by 77 companies revealed by these surveys were in 23 disease categories.

PMA member companies will invest an estimated $7.3 billion this year in research and development. It is clear from these surveys that an increasing share of this research is going into the chronic diseases associated with aging.

With these surveys, we have gained insight into the enormous commitment of the pharmaceutical industry to developing important new drugs for the treatment of diseases that plague our older citizens. In the next few years, as these products emerge from the industry's research pipeline, we will see important advances on this critical medical frontier.

Gerald J. Mossinghoff, *President*
Pharmaceutical Manufacturers Association

Other Medicines for Older Americans

Alzheimer's Disease

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Zacopride	A.H. Robins (Richmond, VA)	(See also Parkinson's disease)	Phase II
Guanfacine	A.H. Robins (Richmond, VA)	(See also Parkinson's disease)	Phase II
BMY 21502	Bristol-Myers (New York, NY)	adjunct to therapy; cognition enhancement	Phase I
DuP 996	DuPont (Wilmington, DE)	cognition enhancement	Phase I
Milacemide	G.D. Searle & Co. (Chicago, IL)		Phase II
HP 029	Hoechst-Roussel (Somerville, NJ)		Phase II
HP 128	Hoechst-Roussel (Somerville, NJ)		Phase II
HOE 427	Hoechst-Roussel (Somerville, NJ)		Phase I/II
Nimotop®** Nimodipine	Miles, Inc. (Elkhart, IN)		Phase III
Acetyl-L-Carnitine	Sigma-Tau, Inc. (Newport Beach, CA)		Phase I
Oxiracetam	SmithKline Beckman (Philadelphia, PA)		Phase II/III
Capoten** Captopril	Squibb (Princeton, NJ)		Phase II
SQ 29 852**	Squibb (Princeton, NJ)		Phase II
Avan Idebenone	TAP Pharmaceuticals (N. Chicago, IL)		Phase I
Tacrine	Warner-Lambert (Morris Plains, NJ)		Phase III

Parkinson's Disease

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Zacopride	A.H. Robins (Richmond, VA)	(See also Alzheimer's disease)	Phase II
Guanfacine	A.H. Robins (Richmond, VA)	(See also Alzheimer's disease)	Phase II
Talipexole	Boehringer Ingelheim Pharmaceuticals (Ridgefield, CT)		Phase II
Motilium® Domperidone	Janssen Pharmaceutica (Piscataway, NJ)	adjunct to therapy (See also adult onset diabetes)	Phase III
SK&F 101468	SmithKline Beckman (Philadelphia, PA)		Phase II
Eldepryl Selegiline Hydrochloride	Somerset Pharmaceuticals, Inc. (Danville, NJ)		application submitted

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**approved by the FDA for other indications

Rheumatoid Arthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Dysprosium Dy–165 FHMA	Cadema Medical Products (Middletown, NY)		Phase II
CGS10787D Prinomide	Ciba-Geigy (Summit, NJ)		Phase III
Voltaren®** Diclofenac sodium	Ciba-Geigy (Summit, NJ)	once-a-day regimen (See also osteoarthritis)	Phase III
Tenoxicam	Marion Laboratories (Kansas City, MO)		Phase III
CP–66, 248	Pfizer (New York, NY)	(See also osteoarthritis)	Phase III
Azulfidine EN-tabs** Sulfasalazine	Pharmacia (Piscataway, NJ)		application submitted
Tifurac Sodium	Syntex (Palo Alto, CA)	(See also osteoarthritis)	Phase II
RS–61443	Syntex (Palo Alto, CA)		Phase I
SPIRO–32® Spirogermanium	Unimed (Somerville, NJ)		Phase I
Durapro® Oxaprozin	Wyeth-Ayerst (Philadelphia, PA) G.D. Searle & Co. (Chicago, IL)	(See also osteoarthritis, gout)	application submitted
Ultradol® Etodolac	Wyeth-Ayerst (Philadelphia, PA)	(See also osteoarthritis, gout)	application submitted
XomaZyme–H65* MAb	XOMA (Berkeley, CA)		Phase I

Gout

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Durapro® Oxaprozin	Wyeth-Ayerst (Philadelphia, PA) G.D. Searle & Co. (Chicago, IL)	(See also osteoarthritis, rheumatoid arthritis)	application submitted
Ultradol® Etodolac	Wyeth-Ayerst (Philadelphia, PA)	(See also osteoarthritis, rheumatoid arthritis)	application submitted

Adult Onset Diabetes

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
HOE 490 Glimepiride	Hoechst-Roussel (Somerville, NJ)		Phase I
Statil Ponalrestat	ICI Pharmaceuticals (Wilmington, DE) Merck, Sharp & Dohme (Rahway, NJ)	adjunct to therapy; aldose reductase inhibitor	Phase III
Motilium® Domperidone	Janssen Pharmaceutica (Piscataway, NJ)	adjunct to therapy (See also Parkinson's disease)	application submitted
Alredase Tolrestat	Wyeth-Ayerst (Philadelphia, PA)		Phase III/application submitted

Osteoarthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Deflazacort	Merrell Dow (Cincinnati, OH)		Phase II
CP–66, 248	Pfizer (New York, NY)	(See also rheumatoid arthritis)	Phase III
Tifurac Sodium	Syntex (Palo Alto, CA)	(See also rheumatoid arthritis)	Phase II
Durapro® Oxaprozin	Wyeth-Ayerst (Philadelphia, PA) G.D. Searle & Co. (Chicago, IL)	(See also rheumatoid arthritis, gout)	application submitted
Ultradol® Etodolac	Wyeth-Ayerst (Philadelphia, PA)	(See also rheumatoid arthritis, gout)	application submitted

Osteoporosis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Ogen** Estropipate	Abbott Laboratories (N. Chicago, IL)		Phase III
Gestodene	Berlex Laboratories (Wayne, NJ)		Phase II
IGF–1*/**	Chiron Corporation (Emeryville, CA) Ciba-Geigy (Summit, NJ)		Phase I
Estraderm® Estradiol transdermal system	Ciba-Geigy (Summit, NJ)		Phase III
Osteo–F Fluoride	Colgate-Hoyt (Canton, MA)		Phase III
Humatrope*/** Somatropin	Eli Lilly (Indianapolis, IN)		in clinical trials
Slow-Fluoride sodium fluoride	Mission Pharmacal (San Antonio, TX)		application submitted
ORTHO-EST	Ortho Pharmaceuticals (Raritan, NJ)		Phase III
ORTHO-EST PLUS	Ortho Pharmaceuticals (Raritan, NJ)		Phase III
Salmon Calcitonin	Rorer Group (Fort Washington, PA)	intranasal dosage form; approved in injectable dosage form under brand name Calcimar®	Phase III

Rheumatoid Arthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Relafen Nabumetone	Beecham Laboratories (Bristol, TN)	(See also osteoarthritis)	Phase III/application submitted
Superoxide Dismutase*	Bio-Technology General (New York, NY)	(See also osteoarthritis)	Phase I
Immuneron®* Recombinant Gamma Interferon	Biogen (Cambridge, MA)		Phase II

Depression

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Aropax	Beecham Laboratories (Bristol, TN)		Phase III
Prothiaden® Dothiepin Hydrochloride	The Boots Company (Lincolnshire, IL)		Phase III
Gepirone	Bristol-Myers (New York, NY)		Phase III
Nefazodone	Bristol-Myers (New York, NY)		Phase III
Wellbutrin® Bupropion Hydrochloride	Burroughs Wellcome (Research Triangle Park, NC)		application submitted
GR50360	Glaxo (Research Triangle Park, NC)		Phase I/II
Moclobemide	Hoffmann-La Roche (Nutley, NJ)		Phase II
ICI–169369	ICI Pharmaceuticals (Wilmington, DE)		Phase II
Ritanserin	Janssen Pharmaceutica (Piscataway, NJ)		Phase II
Maxitene Femoxetine	Martec Pharmaceutical (Kansas City, MO)		Phase II
Etonin™ Etoperidone	McNeil Pharmaceutical (Spring House, PA)		Phase III
ORG 3770	Organon (West Orange, NJ)		Phase III
Sertraline	Pfizer (New York, NY)		application submitted
Fluvoxamine	Reid-Rowell, Inc. (Marietta, GA)		Phase III
Deracyn™ Tablets Adinazolam Mesylate	Upjohn (Kalamazoo, MI)		application submitted
Venlafaxine Hydrochloride	Wyeth-Ayerst (Philadelphia, PA)		Phase III

Osteoarthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Bromfenac	A.H. Robins (Richmond, VA)		Phase II
Relafen Nabumetone	Beecham Laboratories (Bristol, TN)	(See also rheumatoid arthritis)	Phase III/application submitted
Superoxide Dismutase*	Bio-Technology General (New York, NY)	(See also rheumatoid arthritis)	Phase I
Voltaren®** Diclofenac sodium	Ciba-Geigy (Summit, NJ)	once-a-day regimen (See also rheumatoid arthritis)	Phase III
Ontosein® Superoxide Dismutase—Orgotein	DDI Pharmaceuticals (Mountain View, CA)		Phase III

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*genetically engineered

Glaucoma

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Optipress Carteolol	Burroughs Wellcome (Research Triangle Park, NC)		application pending
Ketanserin Ophthalmic	IOLAB Pharmaceuticals (Claremont, CA)		Phase I
Timpilo®	Merck, Sharp & Dohme (West Point, PA)		Phase III

The content of this chart has been obtained through industry sources based on the latest information. Chart current as of January 20, 1989. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. For general information, contact the Pharmaceutical Manufacturers Association at (202) 835-3463. *(If you did not receive your own copy of this issue of "Other Medicines For Older Americans," please write to the Communications Division at the Pharmaceutical Manufacturers Association.)*

GLOSSARY

Adjunct—A substance or drug that aids or helps another become effective or more effective. An adjunct also aids the delivery of a drug to a place where it is most effective in the body.

Aldose reductase inhibitor—a category of drugs being developed to interfere with a series of biochemical and pathological reactions. Their use is intended to prevent the enzyme aldose reductase from changing blood sugar to sorbitol, interrupting the build-up of sorbitol in tissues and preventing cell destruction.

Application submitted—An application for marketing has been submitted by the company to the Food and Drug Administration (FDA).

Phase I—Safety testing and pharmacological profiling in humans.

Phase II—Effectiveness testing in humans.

Phase III—Extensive clinical trials in humans.

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APPENDIX 2

Drug Development Process

It will take an average of 10 years and $125 million for one of these new medicines to go from the laboratory through human testing, and the Food and Drug Administration (FDA) evaluation, and into the pharmacy where physicians can prescribe it.

The first step is compound discovery. Four thousand compounds are screened to find one that has an appropriate biological activity and safety profile. When a lead compound is found, it is evaluated by animal testing to look for evidence of toxicity, carcinogenicity or mutagenicity. This process of preclinical development takes an average of 1.5 years.

The drug then goes into human testing, which consists of three phases.

Phase I studies are conducted in about 50 healthy volunteers, not patients, and take about a year. These studies determine safe dosage range, how the drug is absorbed, distributed, metabolized and excreted, and the duration of its action.

Phase II and III studies are conducted in patients who have the disease that is being investigated. Phase II assesses the drug's effectiveness in about 300 volunteers and takes about two years. Parallel animal and human studies continue during this phase to determine safety.

In Phase III, which lasts about three years, 1,000 to 3,000 patients are tested to identify adverse reactions and confirm earlier efficacy studies. In both Phase II and III, activities continue in manufacturing process development, formulation stability, animal toxicology studies and pharmacokinetic and pharmacodynamic assessments.

After completion of Phase III, the drug sponsor must file a New Drug Application (NDA) with the FDA. An NDA typically contains thousands of pages of information that the sponsor has gathered about the new medicine. Although the FDA tries to review a properly prepared NDA in six months, the average review time in recent years has been about 31 months. If the FDA determines that the NDA contains evidence of safety and effectiveness, the drug company is given approval to manufacture and market the new medicine.

It should be noted that many new drugs are tested on a large number of older patients because they are the people who have the disease being studied. The FDA has confirmed that today's NDAs contain data on an appropriate number of older people.

Generally Accepted Medical Practice

Prescribing marketed drugs for uses not in the labeling approved by the FDA has long been considered acceptable medical practice. When the FDA approves an NDA, it dictates the exact content of the drug's label, which appears verbatim in publications like the Physicians Desk Reference and includes information for the physician on how to use the medication.

The FDA, however, does not attempt to define or regulate "Generally Accepted Medical Practice"; therefore, standard medical practice also includes "off-label usage of approved drugs." The reason for this is that current medical practice is frequently ahead of the FDA regulatory label.

Some physicians are reluctant to use a drug for unlabeled indications even though the indication represents state-of-the-art medical practice. One formal way of assessing Generally Accepted Medical Practice is to refer to three authoritative compendia that list both labeled and unlabeled prescribing indications: 1) U.S. Pharmacopeia Dispensing Information (USP DI), 2) American Hospital Formulary Service Drug Information (AHFS DI), and 3) American Medical Association Drug Evaluations (AMA DE). These compendia are compiled by panels of experts who assess the medical literature and reach a consensus about what constitutes Generally Accepted Medical Practice.

The FDA recommends references like the AMA DE, USP DI and AHFS DI as appropriate guides for physicians to consult when prescribing such "off-label usage." Congress has also accepted this process for determining Generally Accepted Medical Practice and has written it into law in the Medicare program's new drug benefit provisions. The Medicare Catastrophic Coverage Act specifically requires the Secretary of Health and Human Services, when establishing use and reimbursement standards, to take into consideration these medical reference books.

NEW DRUG APPROVALS
IN 1988

Presented by the Pharmaceutical Manufacturers Association

January 1989

Review Averages 31.3 Months
20 New Drugs Approved

Pharmaceutical companies in 1988 won approval to provide 20 new drugs to doctors and patients.

Three drugs each for heart disease, cancer, and stroke—diseases that cause the most deaths in the United States—were among the new drugs (new molecular entities) approved by the Food and Drug Administration.

Four of the approvals were "orphan" drugs to treat rare diseases.

The new approvals include:

- **Heart drugs.** 2 for high blood pressure and an imaging agent for cardiovascular problems;
- **Cancer drugs.** 2 for combination use against germ cell testicular cancer and 1 for certain conditions associated with intestinal cancers;
- **Stroke drugs.** 2 brain imaging agents and a treatment for neurologic problems
- **Other drugs.** 2 for ulcers, an antibiotic, a non-sedating antihistamine, 3 for skin problems, 1 for arthritis, and 1 for Parkinson's disease.
- **Orphan drugs.** These are for varicose veins in the esophagus that can rupture and create dangerous bleeding, cystine kidney stones caused by a hereditary condition, and 2 drugs for combination use against germ cell testicular cancer.

These drugs are listed in more detail in the chart inside.

* * *

For the 20 drugs approved in 1988, the Food and Drug Administration required an average review time of 31.3 months, about the same as last year. Review time is the time required for FDA to determine that test data submitted by the sponsoring company fully meets FDA's criteria for safety and effectiveness.

16 of the drugs already had been approved in one or more countries that have approval systems comparable in quality to that of the United States. This does not necessarily mean that FDA review was slower; companies often submit approval applications first to foreign countries.

It is possible, however, to compare the time of U.S. approval with that of the first approval abroad.

That comparison shows a significant United States lag. For the 16 products first approved abroad, average review time in the country of first approval was 11.7 months, compared with an average review time in the United States for those same products of 29.7 months.

PMA believes the U.S. approval system can be made more efficient, and we applaud FDA Commissioner Frank E. Young's efforts to achieve greater efficiency.

* * *

The force behind development of these new drugs is money invested in new drug research, and I am pleased to report the investment in new drug research continues to grow at a rapid pace.

PMA's annual year-end survey showed a record-breaking $6.5 billion invested in new drug research and development by PMA member firms in 1988, a $1 billion increase over 1987.

We project this strong growth to continue in 1989 and reach $7.3 billion. That means the pharmaceutical industry alone will spend more on research and development this year than the National Institutes of Health will spend on all biomedical research. The NIH budget is $7.15 billion.

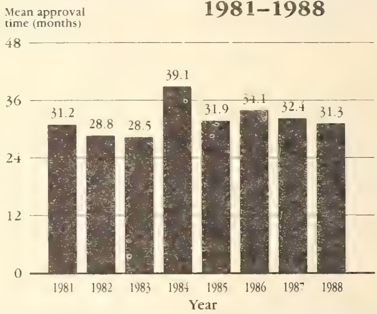
The 1988 R&D investment was 16.3 percent of United States sales and exports. Since 1980, when the ratio was 11.7 percent, the industry has increased the proportion of its sales that are plowed back into research by nearly 40 percent.

Worldwide pharmaceutical sales of PMA member firms were $46.2 billion in 1988, up from $41.6 billion in 1987. $29.9 billion of these sales were in the United States. These R&D and sales statistics are analyzed further in an article on the last page of this chart.

I am convinced, on the basis of this strong growth in research and development, that the productivity of the U.S. pharmaceutical industry will continue, and that if we maintain the current momentum, we will see discoveries of new medicines in the next decade that will have a profound effect upon treatment of diseases of all kinds.

Gerald J. Mossinghoff, *President*
Pharmaceutical Manufacturers Association

Mean Approval Times for New Drugs 1981–1988



Total number of new drugs approved in each year

Source: U.S. Food and Drug Administration

Note: A six-month review time is the statutory standard

New Drug Approvals in 1988

PRODUCT NAME	COMPANY	INDICATION/USE	NDA SUBMITTED	FDA APPROVED	REVIEW TIME	FOREIGN AVAILABILITY
Axid (1C) (nizatidine)	**Eli Lilly (Indianapolis, IN)**	**duodenal ulcers**	**5/12/86**	**4/12/88**	**23 months**	11 countries including: 1987 UK 1988 Denmark 1988 Italy 1988 Netherlands 1988 Canada 1988 Switzerland 1988 France
DESCRIPTION:	For the treatment of active duodenal ulcers and the maintenance of healed duodenal ulcers. It is an oral medication belonging to the class of therapeutic agents known as H_2-receptor antagonists which decrease production of stomach acid associated with duodenal ulcers. (*Contact:* Ed West, 317/276-2000)					
Cardene (1C) (nicardipine hydrochloride)	**Syntex (Palo Alto, CA)**	**hypertension, chronic stable angina**	**11/14/85**[1] **2/20/87**	**12/21/88**	**37 months** **22 months**	17 countries including: 1982 Japan 1984 Italy 1985 France 1986 UK 1986 Belgium
DESCRIPTION:	A calcium-channel blocker used for the treatment of chronic stable angina and hypertension. (*Contact:* Michele Moore, 415/855-5567)					
Cartrol (1C) (carteolol hydrochloride)	**Abbott Labs (N. Chicago, IL)**	**hypertension**	**10/16/84**	**12/28/88**	**50.5 months**	11 countries including: 1981 Japan 1982 W. Germany
DESCRIPTION:	Once-a-day beta-blocker used for the treatment of hypertension. (*Contact:* Jeff Newton, 312/937-5968)					
Ceradon (1C) (cefotiam hydrochloride)	**Takeda Chemical Industries (Osaka, Japan)**	**cephalosporin antibiotic**	**4/30/85**	**12/30/88**	**44 months**	Total not available 1981 Japan
DESCRIPTION:	For treating lower respiratory tract infections, bronchitis and pneumonia. (*Contact:* Jeffrey McMullen, G.H. Besselaar Associates—which conducted clinical trials and prepared the NDA in the United States on behalf of Takeda—609/452-8550)					
Ceretec (1B) (exametazime in a kit for use with technetium Tc99m)	**Amersham Corp. (Arlington Heights, IL)**	**nuclear medicine brain imaging agent**	**3/14/88**	**12/30/88**	**9.5 months**	7 countries including: 1986 Canada 1987 UK 1987 Denmark 1987 Belgium 1987 France 1988 Sweden
DESCRIPTION:	Used as an adjunct with technetium in imaging regional blood flow through the brain. Assists in diagnosing the extent of stroke damage and in evaluating TIAs (transient ischemic attacks) that occur when brain arteries are temporarily blocked. (*Contact:* William Ehmig, 312/593-6300, ext. 244)					
Cytotec (1A) (misoprostol)	**Searle (Chicago, IL)**	**prevention of stomach ulcers**	**5/23/84** **3/11/88**	**12/27/88**	**9.5 months**[2]	43 countries including: 1985 Mexico 1985 Switzerland 1986 Canada 1986 W. Germany 1987 France 1988 UK
DESCRIPTION:	A synthetic prostaglandin used for the prevention of stomach ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs) that are used to treat arthritis. (*Contact:* Gregory Baird, 312/470-6700)					
Ethamolin (1B) (ethanolamine oleate) *Orphan*	**Glaxo (Research Triangle Park, NC)**	**treatment of esophageal varices**	**9/14/84**	**12/22/88**	**51 months**	USA first marketing for this indication
DESCRIPTION:	For treating internal bleeding caused by esophageal varices, which are varicose veins in the lower esophagus that sometimes rupture, creating dangerous bleeding. (*Contact:* Jennifer McMillan, 919/248-2392)					

NOTE: Numbers and letters in parentheses after the drug names indicate the following:

Chemical Type **(as classified by the U.S. Food and Drug Administration)**

1 = *New Molecular Entity*—the active moiety has not been previously marketed (either as the parent compound or as a salt, ester or derivative of the parent compound) in the United States for use in a drug product either as a single ingredient or part of a combination.

4 = *New combination*—the product contains two or more compounds which have not previously been marketed together in a drug product in the United States by any manufacturer.

Therapeutic Potential Ratings **(as classified by the FDA)**

A = Important therapeutic gain.
B = Modest therapeutic gain.
C = Little or no therapeutic gain.

FOOTNOTES:

(1) Original submission in 1985 was for angina claim; amended in 1987 for hypertension. FDA approval was for both indications.
(2) Calculated from 3/11/88, the submission date of amendment for indication approved on 12/27/88.

GLOSSARY

Agonist—A drug that combines with a receptor prior to drug action.

Allylamine—A class of organic, alkaline compounds.

Aneurysm—An abnormal dilation of a blood vessel.

Angina—Severe chest pain caused by insufficient oxygen in the heart muscle.

Angiography—An imaging technique to study the structure of blood vessels.

Antagonist—A substance that opposes the action of another substance.

Antihypertensive—A substance which lowers high blood pressure.

Calcium-channel blocker—A substance which acts on the cardiovascular system to lower blood pressure by relaxing smooth muscle in the walls of arteries.

Carcinoid tumors—Slow-growing tumors characterized by secretion of peptides such as serotonin. Usually found in the small intestine.

Cerebral imaging—Taking pictures of the brain to diagnose abnormalities.

Chronic stable angina—Angina brought on by exertion (as compared to angina that occurs at rest).

Contrast medium—A substance used to enhance x-ray images of organs and spaces in the body.

CT—Computerized Tomography: A method of imaging in which a computer is used to produce higher quality images of body parts.

Cystine—An amino acid that can form kidney stones in certain patients.

Cystitis—Inflammation of the urinary bladder.

Dopamine—A naturally occurring chemical in the body involved in several biological processes, including the neurologic regulation of body movement.

Dopamine agonist—A substance which mimics the action of dopamine.

Duodenum—The first portion of the small intestine.

FDA—Food and Drug Administration.

Hemorrhage—Excessive bleeding.

Hypertension—High blood pressure.

Idiopathic—Denotes a disease of unknown cause.

Ischemia—Insufficient blood supply to a body part or organ. For example, brain ischemia can result in TIAs (transient ischemic attacks) or reversible stroke-like conditions.

Lesion—A tissue abnormality.

Moiety—The part of a molecule that exerts a medical effect.

MRI—Magnetic resonance imaging: A method of imaging the brain without using ionizing radiation to diagnose abnormalities.

Non-ionic—A molecule that does not dissociate into positively and negatively charged particles when dissolved in water.

Paramagnetic enhancement agent—A substance that enhances imaging of the brain.

Peptide—A compound containing two or more amino acids.

Prostaglandin—A family of compounds that has many effects, including inhibition of inflammation and protection of the stomach lining.

Rhinitis—Inflammation of the mucous membranes in the nose.

Subarachnoid—The space between the brain and a membrane covering the brain.

TIAs—Transient ischemic attacks: Reversible stroke-like conditions.

Uroprotectant—A substance that protects the lining of the bladder.

Urticaria—Hives.

UVA, UVB rays—Ultraviolet rays of differing wave lengths.

Vasoactive intestinal peptide (VIP) secreting tumors—Slow-growing tumors, usually found in the pancreas, that secrete VIP in excessive amounts and result in a profuse, watery diarrhea.

Provided as a Public Service by the Pharmaceutical Manufacturers Association.

The Drug Approval Process

The U.S. system of new drug approvals is perhaps the most rigorous in the world. Here is how a drug is tested and approved.

Preclinical Testing. The promising agent is first subjected to extensive laboratory and animal testing to determine answers to two key questions: Is the compound biologically active? Is it safe? If the answers to both appear to be affirmative, the drug sponsor is ready to test in humans. This stage generally lasts from one to two years.

Investigational New Drug. Before human tests can start, the drug sponsor must file an Investigational New Drug (IND) application with the Food and Drug Administration (FDA), showing the results of all animal testing and how the drug is made. The IND becomes effective if FDA does not disapprove the application in 30 days.

Human Testing (Clinical). There are three phases of human testing, each involving larger numbers of people than the one before.

Phase I. Safety Studies and Pharmacological Profiling: This phase determines the drug's pharmacological actions, its safe dosage range, how it is absorbed, distributed, metabolized and excreted, and the duration of its action. These tests involve a small number of normal healthy subjects (not patients). Phase I clinical testing can usually be conducted in less than one year.

Phase II. Pilot Efficacy Studies: This phase consists of controlled studies in approximately 200 to 300 volunteer patients to assess the drug's effectiveness. Simultaneous animal and human studies continue to determine the drug's safety. Phase II clinical testing may require about two years to complete.

Phase III. Extensive Clinical Trials: Here the testing moves to larger numbers of volunteer patients, usually 1,000 to 3,000, in clinics and hospitals. The drug is administered by practicing physicians to those suffering from the condition the drug is intended to treat. These studies must confirm earlier efficacy studies and identify low-incidence adverse reactions. Phase III clinical trials last about three years.

New Drug Application (NDA). Following completion of Phase III, the drug sponsor must file an NDA with the FDA, containing all the information the sponsor has gathered. NDAs typically run into thousands of pages. The information submitted must include the chemical structure of the drug, scientific rationale and purpose, animal and laboratory studies, results of all tests in humans, formulation and production details, and proposed labeling. On average, the NDA review and approval process by FDA takes two to three years.

Approval. Once an NDA is approved, the company is required to periodically submit reports to FDA, including adverse reaction data and production, quality control and distribution records. For some drugs, FDA requires affirmative postmarketing monitoring, or additional studies to evaluate the long-term effects.

PRODUCT NAME	COMPANY	INDICATION/USE	NDA SUBMITTED	FDA APPROVED	REVIEW TIME	FOREIGN AVAILABILITY
Optiray (1C) (ioversol)	**Mallinckrodt (St. Louis, MO) (a subsidiary of International Minerals & Chemical Corp.)**	**imaging agent**	**6/25/87**	**12/30/88**	**18 months**	USA first marketing
DESCRIPTION:	Non-ionic contrast medium used for angiography of the cardiovascular system and brain, CT (computed tomography) imaging, and images of the urinary tract. (*Contact:* Dr. Patricia Hicks, 314/895-2077)					
Oxistat (1C) (oxiconazole nitrate)	**Glaxo (Research Triangle Park, NC)**	**various fungal skin infections**	**2/11/88**	**12/30/88**	**10.5 months**	26 countries including: 1984 W. Germany 1985 Japan 1985 Switzerland 1986 Finland
DESCRIPTION:	A topical anti-fungal used to treat athlete's foot, body ringworm and groin dermatitis. (*Contact:* Jennifer McMillan, 919/248-2392)					
Permax (1B) (pergolide mesylate)	**Eli Lilly (Indianapolis, IN)**	**adjunctive treatment for the signs and symptoms of Parkinson's disease**	**9/11/85**	**12/30/88**	**39.5 months**	USA first marketing
DESCRIPTION:	Used with levodopa/carbidopa medication to treat the signs and symptoms of Parkinson's disease. It belongs to a class of drugs known as dopamine agonists. (*Contact:* Ed West, 317/276-2000)					
Photoplex (1,4C) (butyl methoxydibenzoylmethane and padimate-o)	**Herbert Laboratories (Santa Ana, CA) (a division of Allergan, Inc.)**	**sunscreen (over-the-counter)**	**3/29/85**	**9/30/88**	**42 months**	USA first marketing in this combination at these concentrations
DESCRIPTION:	Broad spectrum sunscreen lotion for providing year-round protection from the damaging effects of ultraviolet radiation. It provides protection from UVB and UVA rays. (*Contact:* Stacey Howmann, 714/458-5134)					
Sandostatin (1A) (octreotide acetate)	**Sandoz (East Hanover, NJ)**	**diarrhea associated with certain cancers**	**2/6/87**	**10/21/88**	**20.5 months**	Total not available 1988 New Zealand 1988 Netherlands 1988 Denmark 1988 Switzerland
DESCRIPTION:	For treating severe and unrelenting diarrhea associated with rare forms of intestinal endocrine cancer, namely, malignant carcinoid tumors and vasoactive intestinal peptide (VIP) secreting tumors. It is a synthetic peptide which mimics the action of the digestive tract hormone somatostatin. (*Contact:* Dr. Joseph A. Romano, 201/503-7165)					
Thiola (1B) (tiopronin) *Orphan*	**University of Texas (Dallas, TX)**	**prevention of kidney stone formation**	**1/8/86**	**8/11/88**	**31 months**	9 countries including: 1962 Japan 1970 Italy 1975 Belgium 1977 W. Germany
DESCRIPTION:	For the prevention of cystine kidney stone formation in patients with severe homozygous cystinuria, a hereditary condition of persistant, excessive urinary secretion of cystine and other amino acids. (*Contact:* Dan Crawford, Mission Pharmacal—which holds the marketing rights in the United States—1-800/531-3333)					
Voltaren (1C) (diclofenac sodium)	**Ciba-Geigy (Summit, NJ)**	**arthritis**	**12/20/83**	**7/28/88**	**55 months**	120 countries including: 1974 Japan 1974 Switzerland 1975 France 1975 Italy 1975 Belgium 1976 W. Germany 1978 UK 1980 Canada 1981 Sweden
DESCRIPTION:	A nonsteroidal anti-inflammatory drug (NSAID) used to treat arthritis. NSAIDs are thought to work by inhibiting prostaglandin production, thus reducing inflammation and the swelling and pain common to arthritis. (*Contact:* Cathy Kernen, 201/277-7158)					

The content of this chart has been obtained through government and industry sources. For more specific information about a particular product, call the contact person listed for each drug. For general information, contact the Pharmaceutical Manufacturers Association at (202) 835-3463.

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PRODUCT NAME	COMPANY	INDICATION/USE	NDA SUBMITTED	FDA APPROVED	REVIEW TIME	FOREIGN AVAILABILITY
Hismanal (1C) (astemizole)	**Janssen Pharmaceutica (Piscataway, NJ)**	**non-sedating antihistamine**	**2/25/85**	**12/29/88**	**46 months**	105 countries including: 1983 UK 1983 Belgium 1983 Switzerland 1984 Canada 1984 W. Germany 1985 France 1985 Italy 1985 Netherlands
DESCRIPTION:	For relief of symptoms associated with seasonal allergic rhinitis, such as hay fever, and chronic idiopathic urticaria, or hives. (*Contact:* Roger Aspeling, 201/524-9703)					
Ifex (1A) (ifosfamide) *Orphan*	**Bristol-Myers (New York, NY)**	**testicular cancer**	**12/10/87**	**12/30/88**	**12.5 months**	about 30 countries including: 1976 France 1978 UK 1978 Italy 1979 Switzerland 1979 Netherlands 1981 Belgium 1985 Japan 1988 Canada
DESCRIPTION:	Used in combination with other anti-cancer drugs for germ cell cancer of the testis. Should ordinarily be used with a uroprotectant, such as Mesnex (mesna), also approved in 1988, which prevents hemorrhagic cystitis. (*Contact:* Bristol-Myers U.S. Pharmaceutical Group, 812/429-5000)					
Magnevist (1B) (gadopentetate dimeglumine)	**Berlex Laboratories, Inc. (Wayne, NJ)**	**cerebral imaging**	**8/19/86**	**6/2/88**	**21.5 months**	7 countries including: 1988 W. Germany 1988 Austria 1988 Belgium 1988 Sweden 1988 Netherlands 1988 Norway
DESCRIPTION:	For imaging lesions in the brain. It is the first paramagnetic enhancement agent for MRI. (*Contact:* Jack Malpass, 201/694-4100)					
Mesnex (1B) (mesna) *Orphan*	**Asta Pharma AG (Degussa) (Frankfurt, W. Germany)**	**prevention of hemorrhagic cystitis**	**6/30/88**	**12/30/88**	**6 months**	about 30 countries including: 1979 W. Germany 1980 Netherlands 1981 Switzerland 1982 Belgium 1983 UK 1985 Italy 1988 Canada
DESCRIPTION:	Used as a uroprotectant to reduce the incidence of ifosfamide-induced hemorrhagic cystitis. Used with Ifex (ifosfamide), also approved in 1988. (*Contact:* Bristol-Myers U.S. Pharmaceutical Group—which will distribute Mesnex in the United States—812/429-5000)					
Naftin (1C) (naftifine hydrochloride)	**Herbert Laboratories (Santa Ana, CA) (a division of Allergan, Inc.)**	**antifungal**	**3/8/86**	**2/29/88**	**23.5 months**	18 countries including: 1984 Austria 1985 W. Germany 1985 Switzerland
DESCRIPTION:	An antifungal used to treat skin fungi. First in a new class of synthetic antifungal agents, the allylamines. (*Contact:* Stacey Howmann, 714/458-5134)					
Nimotop (1A) (nimodipine)	**Miles, Inc. (Elkhart, IN)**	**treatment of neurological damage due to spasm**	**9/16/82**	**12/28/88**	**75.5 months**	27 countries including: 1985 W. Germany 1985 Finland 1986 Austria 1987 Switzerland 1987 France 1987 Denmark 1988 UK
DESCRIPTION:	A calcium-channel blocker used for the treatment of neurological damage due to spasm of cerebral arteries caused by subarachnoid hemorrhage. (*Contact:* Joseph A. D'Arco, 203/937-2401)					

16% of Sales Devoted To Research

Industry Adds $1 Billion to R&D Spending

The U.S. pharmaceutical industry invested a record $6.5 billion in research and development in 1988—$1 billion more than its 1987 expenditure of $5.5 billion. This represents an 18.2 percent increase.

Projections for 1989 indicate that this trend will continue. Estimated spending for research and development in 1989 is $7.3 billion.

Research and development investment by the pharmaceutical industry has increased steadily in recent years, nearly doubling every five years. Moreover, as a percentage of U.S. sales and exports, U.S. research and development expenditures have increased by nearly 40 percent since 1980. Expenditures went from 11.7 percent of sales and exports in 1980 to 16.3 percent in 1988.

The findings indicate that pharmaceutical companies are continuing to expand research programs to take advantage of new opportunities in molecular biology, including biotechnology advances.

Following is a detailed account of the industry's commitment to pharmaceutical research and development since 1983:

R&D Spending By PMA Members

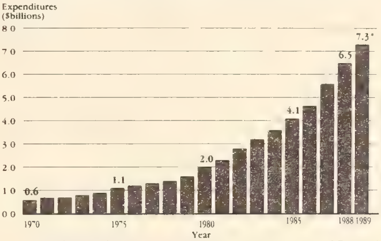
	U.S.	Worldwide	U.S. R&D as % of Sales + Exports **
1989*	$5.8B	$7.3B	16.2%
1988*	5.2	6.5	16.3
1987	4.5	5.5	15.8
1986	3.9	4.7	14.8
1985	3.4	4.1	14.8
1984	3.0	3.6	14.4
1983	2.7	3.2	14.4

* Estimated figures

** U.S. Exports 1989: $2.3 billion (estimated)

The pharmaceutical industry also achieved record sales in 1988, according to PMA estimates. Worldwide pharmaceutical sales of PMA member companies reached $46.2 billion, an 11 percent increase over the 1987 figure of $41.6 billion. Sixty-five percent of these sales—$29.9 billion—were in the United States.

R&D Investments by PMA Member Firms



Source: PMA Annual Survey

* Estimated

Worldwide sales for PMA member firms are estimated to be $51.5 billion in 1989. Two-thirds of that figure is expected to be U.S. sales.

Here is an in-depth listing of U.S., foreign, and worldwide sales figures for the research-based pharmaceutical industry:

Worldwide Pharmaceutical Sales of PMA Member Firms

	U.S.	Foreign	Total	% U.S.
1989*	$33.8B	$17.7B	$51.5B	66%
1988*	29.9	16.3	46.2	65
1987	26.6	15.1	41.6	64
1986	24.1	13.0	37.1	65
1985	21.1	10.9	32.0	66
1984	19.4	10.5	29.9	65
1983	17.1	10.4	27.5	62

(Sales include dosage-form, bulk, and veterinary products)

* Estimated figures

PMA collected the information on research investment and sales in an annual survey of its more than 100 member companies, which discover and develop the vast majority of the prescription drugs in the United States.

**Pharmaceutical
Manufacturers
Association**

1100 15th Street, NW • Washington, DC 20005 • Telephone (202) 835-3400

Mr. Downey. Thank you.

Mr. Fair.

STATEMENT OF RUSSELL B. FAIR

Mr. Fair. Good afternoon, Mr. Chairman. On behalf of Giant Food, I want to thank you for allowing us this opportunity to present our drug interaction system.

The Giant Pharmacy Computer System, PROFILE, has been fully operational since July of 1983. The computer system was seen as the wave of the future, which could be used for competitive advantage by increasing productivity, standardizing prices, maintaining prescription records, and third party administration and billing. The ability to monitor drug interactions and to generate patient drug expenditures were seen as attractive features for customers. In addition, the pharmacy computer system could be used to generate needed reports for pharmacy operations.

The PROFILE maintains customers prescription records and alerts pharmacists to potentially dangerous drug related adverse reactions. All Giant pharmacies operate independently of each other and are unable at the present tme to communicate with each other. All customer information is kept on record—in the computer system, that is—for a minimum of 15 months from the last active date of service.

Giant Food is provided the information for our drug interaction system by Professional Drug Systems, Inc. of St. Louis, MO. The software is marketed under the trade name MEDICOM. MEDICOM was chosen for its reputation as a leader in this new emerging field, timely updates, 24 hour, 7-day-a-week toll free professional hot line, not only for the pharmacy but for any physician, and an insurance policy on the reliability of the information provided by the software.

Typically, as a customer presents prescriptions to be filled, he or she is asked general questions regarding personal information, generic drug and safety cap preferences, and any third party information, if applicable.

This information is then entered in the computer. Once various edits are completed by the computer, the process of searching for possible adverse drug reactions begins. The prescription being filled is compared to all previously filled prescriptions on record, regardless of data filled. the PROFILE has the ability to not only monitor adverse prescription drug to prescription drug reactions, but also the following: prescription drug to OTC drug; prescription and OTC drug to food/nutrients; prescription and OTC drug to allergy contraindication; and prescription and OTC drug to disease state.

The latter two situations are only possible if the customer has previously completed a medical history form available at our prescription counters. This form asks various questions concerning medical history, allergies, and personal information. Currently, only 17 percent of all our customers in our system have completed such information, despite conscientious company efforts to encourage customer compliance.

In one situation, in a new store opening, we offered $10 for every customer to fill out one of these profiles, and that store only has received a 25 percent compliance rate.

If an adverse drug reaction is found, the following information is displayed to the pharmacist. I have given you an exhibit of a drug reaction that has been submitted to our pharmacy. We have run the ad in the past and we will be running it in 2 to 3 weeks because in just the last week we had three other pharmacies reporting the same drug interaction that I have submitted here to the committee.

In the drug interaction which is displayed to the pharmacist, as is shown on the exhibit, the current customer/physician drug information is displayed, the previous physician, date filled, the previously filled prescription, and gives us source reference manuals used in conjunction with the PROFILE system which contains detailed documentation and references for the adverse drug reactions.

It gives a severity code, a numbering system of five levels, which we use all five, which identifies the severity of the adverse drug reaction to the pharmacist, and it gives also action codes, a system using alpha letter characterizations, suggesting causative action to be taken by the pharmacist.

In the PROFILE system, the two highest severity codes have an on-line display of supplemental information. This may contain all or an abbreviated version of the information contained in the manual. This feature saves valuable time and gives the pharmacist, at a finger's touch, most of the information he/she needs to make a recommendation to the physician or the customer, or both.

The last exhibit displays an action the pharmacist may take in completing the prescription. The pharmacist has the ability to print any of the information displayed to him or her at any time should they not be able to contact the customer or physician at the time of filling.

It is not in every situation in which the customer is present at the drug counter getting a prescription filled. Over half our prescriptions filled are coming in via a phone call or refill situations or something of the like. The customer is not always present at the time that we're reviewing this drug information, so we have to give the ability to our pharmacists to display this information, and make contact with the physician or the patient at a later time.

In conclusion, the Inspector General's report entitled "Medicare Drug Utilization Review" contains many useful recommendations that I concur with. One missing element I found in the report has to do with the colleges of pharmacies and the recommendation that they, too, institute required courses in geriatric studies.

I will entertain any questions you may have.

[The prepared statement of Russell B. Fair follows:]

PREPARED STATEMENT OF RUSSELL FAIR, THIRD PARTY SUPERVISOR, PHARMACY LIAISON, GIANT FOOD, INC.

The Giant Pharmacy Computer System (PROFILE) has been fully operational since July 1983. The computer system was seen as the "wave of the future" which could be used for competitive advantage by increasing productivity, standardizing prices, maintaining prescription records, and third party administration and billing. The ability to monitor drug interactions and to generate patient drug expenditures were seen as attractive features for customers. In addition, the pharmacy computer system could be used to generate needed reports for pharmacy operations.

The PROFILE maintains customers prescription records and alerts pharmacists to potentially dangerous drug related adverse reactions. All Giant pharmacies operate independently of each other and are unable at the present time to communicate with each other. All customer information is kept on record (in the computer) for a minimum of 15 months from the last active date of service.

Giant Food Inc. is provided the information for our drug interaction system by Professional Drug Systems, Inc., of St. Louis Mo. The software is marketed under the trade name MEDICOM. MEDICOM was chosen for its reputation as a leader in this new emerging field, timely updates, 24 hour, 7 day a week toll free professional hotline support, and an insurance policy on the reliability of the information provided by the software.

Typically, as a customer presents prescriptions to be filled, he/she is asked general questions regarding personal information, generic drug and safety cap preferences, and any third party information, if applicable.

This information is then entered in the computer. Once various edits are completed by the computer, the process of searching for possible adverse drug reactions begins. The prescription being filled is compared to all previously filled prescriptions on record regardless of date filled. The PROFILE has the ability to not only monitor adverse prescription drug to prescription drug reactions, but also the following:

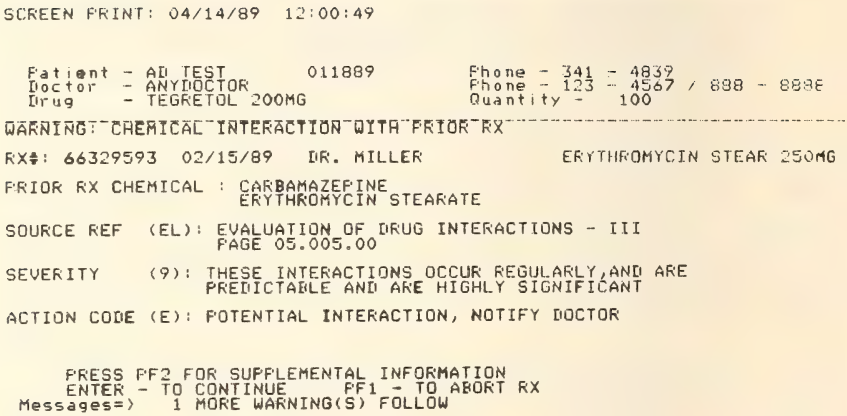
- Prescription drug to OTC drug.
- Prescription and OTC drug to food/nutrients.
- Prescription and OTC drug to allergy contraindication.
- Prescription and OTC drug to disease state.

The latter two situations are only possible if the customer has previously completed a medical history form available at the prescription counter. This form asks various questions concerning medical history, allergies, and personal information. Currently only 17% of all customers in our system have completed such information, despite conscientious company efforts to encourage customer compliance.

If an adverse drug reaction is found , the following information is displayed to the Pharmacist: (See exhibit 1)

- Customer, physician, drug information.
- Physician, date filled, drug from previously filled prescription.
- Source Reference: Manuals used in conjunction with the PROFILE system which contains detailed documentation and references for the adverse drug reactions.
- Severity Code: A numbering system (5 levels) which identifies the severity of the adverse drug reaction to the Pharmacist.
- Action Code: A system using alpha (letters) characterizations suggesting courses of action to be taken by the Pharmacist.

Exhibit No 1



```
SCREEN PRINT: 04/14/89  12:00:49


  Patient - AD TEST       011889         Phone - 341 - 4839
  Doctor  - ANYDOCTOR                    Phone - 123 - 4567 / 888 - 8888
  Drug    - TEGRETOL 200MG               Quantity -   100
WARNING: CHEMICAL INTERACTION WITH PRIOR RX------------------------------------

RX#: 66329593  02/15/89   DR. MILLER          ERYTHROMYCIN STEAR 250MG

PRIOR RX CHEMICAL : CARBAMAZEPINE
                    ERYTHROMYCIN STEARATE

SOURCE REF  (EL): EVALUATION OF DRUG INTERACTIONS - III
                  PAGE 05.005.00

SEVERITY    (9): THESE INTERACTIONS OCCUR REGULARLY,AND ARE
                 PREDICTABLE AND ARE HIGHLY SIGNIFICANT

ACTION CODE (E): POTENTIAL INTERACTION, NOTIFY DOCTOR


    PRESS PF2 FOR SUPPLEMENTAL INFORMATION
    ENTER - TO CONTINUE     PF1 - TO ABORT RX
 Messages=)   1 MORE WARNING(S) FOLLOW
```

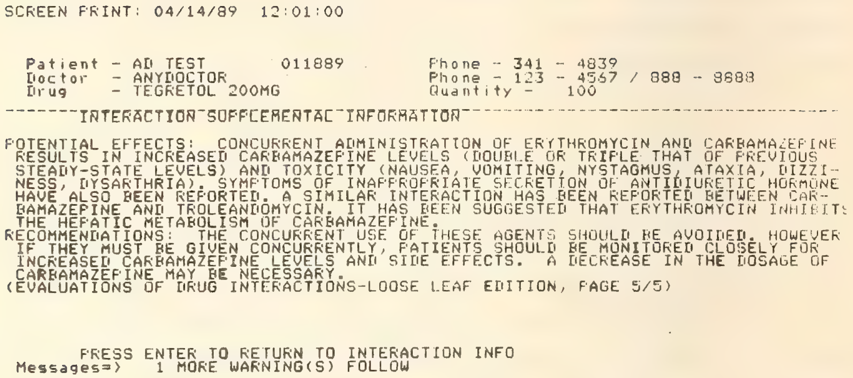
In the PROFILE system the two highest severity codes have an "on-line" display of "supplemental information". This may contain all, or an abbreviated version of the information contained in the manual. This feature saves valuable time and gives the Pharmacist at a fingers touch, most of the information he/she needs to make a recommendations to the physician or customer, or both. (See exhibit 2).

The last exhibit #3, displays an action the Pharmacist may take in completing the prescription. The Pharmacist has the ability to print any of the information displayed to him/her at any time should they not be able to contact the customer or physician at the time of filling.

In conclusion, the Inspector General's report entitled "Medicare Drug Utilization Review" contains many useful recommendations that I concur with. One missing element I found in the report has to do with the Colleges of Pharmacies and the recommendation that they too, institute required courses in geriatric studies.

- 5 -

Exhibit No 2

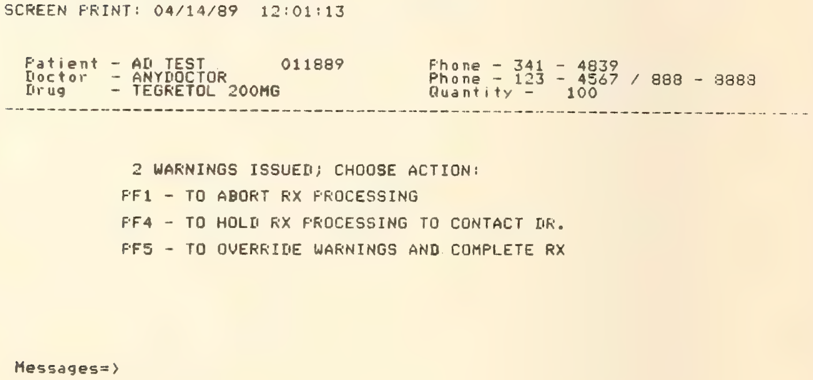


```
SCREEN PRINT: 04/14/89  12:01:00

  Patient  - AD TEST        011889          Phone - 341 - 4839
  Doctor   - ANYDOCTOR                      Phone - 123 - 4567 / 888 - 8888
  Drug     - TEGRETOL 200MG                 Quantity -   100
-------INTERACTION-SUPPLEMENTAL-INFORMATION-----------------------------------
POTENTIAL EFFECTS:  CONCURRENT ADMINISTRATION OF ERYTHROMYCIN AND CARBAMAZEPINE
 RESULTS IN INCREASED CARBAMAZEPINE LEVELS (DOUBLE OR TRIPLE THAT OF PREVIOUS
 STEADY-STATE LEVELS) AND TOXICITY (NAUSEA, VOMITING, NYSTAGMUS, ATAXIA, DIZZI-
 NESS, DYSARTHRIA). SYMPTOMS OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE
 HAVE ALSO BEEN REPORTED. A SIMILAR INTERACTION HAS BEEN REPORTED BETWEEN CAR-
 BAMAZEPINE AND TROLEANDOMYCIN. IT HAS BEEN SUGGESTED THAT ERYTHROMYCIN INHIBITS
 THE HEPATIC METABOLISM OF CARBAMAZEPINE.
RECOMMENDATIONS:  THE CONCURRENT USE OF THESE AGENTS SHOULD BE AVOIDED. HOWEVER
 IF THEY MUST BE GIVEN CONCURRENTLY, PATIENTS SHOULD BE MONITORED CLOSELY FOR
 INCREASED CARBAMAZEPINE LEVELS AND SIDE EFFECTS.  A DECREASE IN THE DOSAGE OF
 CARBAMAZEPINE MAY BE NECESSARY.
(EVALUATIONS OF DRUG INTERACTIONS-LOOSE LEAF EDITION, PAGE 5/5)


      PRESS ENTER TO RETURN TO INTERACTION INFO
 Messages=>   1 MORE WARNING(S) FOLLOW
```

Exhibit No 3



```
SCREEN PRINT: 04/14/89  12:01:13

  Patient  - AD TEST        011889          Phone - 341 - 4839
  Doctor   - ANYDOCTOR                      Phone - 123 - 4567 / 888 - 8888
  Drug     - TEGRETOL 200MG                 Quantity -   100
------------------------------------------------------------------------------

              2 WARNINGS ISSUED; CHOOSE ACTION:
             PF1 - TO ABORT RX PROCESSING
             PF4 - TO HOLD RX PROCESSING TO CONTACT DR.
             PF5 - TO OVERRIDE WARNINGS AND COMPLETE RX



 Messages=>
```

Mr. DOWNEY. First of all, I want to thank the panel. I again apologize for keeping you waiting.

Your testimony has been very, very helpful to the committee. It is our hope that we can have an ongoing dialogue on a number of the points that were raised here. I am very interested in what Giant is doing as a model for what others may do, and maybe there are lessons for us to learn. As you pointed out, you offered a bounty and it is still not possible to get people to comply with certain things.

Do you have any reason to believe why that's the case?

Mr. FAIR. On our receipts that we give to customers who don't fill out the profile, there is a message there that states no medical history on file. We have asked our pharmacists, each time they see that message, to insert one of these patient profiles in their prescription bag and ask them to mail it in. It's a postage-free type of mailing.

Some of the stores have very high rates of compliance, but they go out and ask the customers to fill out the prescription profile right then and there and almost won't dispense the prescriptions to them until they fill out that profile. In that case, you get very, very high compliance rates. We have some stores that are 60 and 70 percent. But, once again, those are the lower volume pharmacies in which they have to time to go out there and talk to the individuals and asking them to do that type of thing.

Once again, it's a learning curve. But we haven't been able to budge off that learning curve in 2 years of tracking that information.

Mr. DOWNEY. Dr. Beary.

Dr. BEARY. To add to that one strategy, you might consider calling the primary care physician, who would be the person who should have a master drug list that they could share with you. That might be the most efficient way to get it, and also to get an accurate one. Because quite often you take a drug history and people don't have it quite right. They're either not taking exactly what they think they have, or they have left out a few things. So I think that linkage between the pharmacist and the primary care doc is a rather important one.

Mr. DOWNEY. Thank you very much. Thank you all.

The hearing is adjourned.

[Whereupon, at 1:30 p.m., the hearing was adjourned.]

APPENDIX

AP1

THOMAS J. DOWNEY, NEW YORK
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JOHN P. OLINGER
STAFF DIRECTOR
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NATALIE CANNON
MINORITY STAFF DIRECTOR
(202) 226-3349

May 15, 1989

Mr. Richard P. Kusserow
Inspector General
Department of Health and Human Services
Room 5250 Cohen Building
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Kusserow:

I am writing as a follow up to the hearing held on April 19 by the Subcommittee on Human Services on Drug Misuse Among the Elderly and Its Impact on Community Based Care.

You will be delighted to know that we have received much positive feedback since the hearing was held last month, and your participation was greatly appreciated. My staff is in the process of editing testimony in order to submit it as part of the official hearing record. I would be interested in learning whether the final copy of your Drug Utilization Review study has been completed so it also may be included. I feel it would be an essential part of the hearing record, and as you indicated in your testimony, it will be a good benchmark to the American people and to the beneficiary community.

I would appreciate hearing from you as soon as possible. Please do not hesitate to contact me or my Subcommittee staff at 226-3348 if you have any questions.

With best wishes, I am

Sincerely,

Tom J. Downey

THOMAS J. DOWNEY
Chairman
Subcommittee on Human Services

TJD:mb

MEDICARE DRUG UTILIZATION REVIEW

RICHARD P. KUSSEROW
INSPECTOR GENERAL

OAI-01-88-00980

APRIL 1989

EXECUTIVE SUMMARY

PURPOSE AND OBJECTIVES

The overall aim of this inspection was to foster the development and implementation of an effective Drug Utilization Review (DUR) system under the Medicare program. Toward this end, it sought to promote a better understanding of the major problems and needs that a DUR program should address and of the relevant insights that emerge from research and experience.

BACKGROUND

Among the many provisions of the Medicare Catastrophic Coverage Act of 1988 is the one calling for the Department of Health and Human Services (HHS) to establish a Medicare DUR program. This mandate offers the Department a significant opportunity to design and operate a multi-level DUR effort to improve quality of care, avoid unnecessary Medicare and personal expenditures, and maintain program integrity. This report presents information and recommendations that can help the Department take maximum advantage of that opportunity. In so doing, it draws heavily on a review of State Medicaid experience, demonstration efforts, and research findings.

FINDINGS

- There is a widespread problem of mismedication among older adults. That problem is likely to grow when the Medicare drug benefit is implemented, unless an effective DUR program is developed.
    - Although Americans age 60 and over comprise only 17 percent of the total U.S. population, they account for 39 percent of all hospitalizations and 51 percent of deaths from drug reactions.
    - In 1987, at least 200,000 older adults were hospitalized due to adverse drug reactions, or experienced an adverse drug reaction while hospitalized.
- The problem of mismedication among the elderly reflects a series of systemic weaknesses throughout the drug therapy delivery system.
    - At the pharmaceutical manufacturer level, information about appropriate dosage levels and potential adverse reactions related to drugs consumed by older adults is inadequate.
    - At the physician level, there is evidence of widespread prescribing patterns that are suboptimal for older adults. For the most part, this is a product of inadequate training and education for physicians in geriatric pharmacology.

  - At the community pharmacy level, findings indicate that only a small percentage of elderly patients receive drug counseling services even when such services are mandated by State regulations. Further, there is evidence that many community pharmacists do not perform adequate reviews of patients' drug regimens or consult with physicians and patients when potential problems are identified.

  - Many utilization problems occur at the patient level in administration of drug therapy among older adults. Compliance with drug regimen rates range from 38 percent to 57 percent, with an average of 45 percent. Medication behavior problems include underuse and overuse of drugs, sharing of drugs among family and friends, use of outside prescriptions, and use of damaged medications.

- The results of DUR interventions instituted by some State level programs and by researchers and practitioners are relevant to the design of a Medicare DUR program. Significant findings include:

  - Some State programs use post payment review to identify quality of care problems among beneficiaries. Such reviews include automated analyses of patient profiles coupled with case reviews by peer committees. While this method is useful in identifying broad patterns of mismedication, it appears less effective in correcting such problems.

  - The value of linking diagnostic codes with prescriptions for the purpose of DUR analysis is highly questionable.

  - In terms of effecting clinical changes in physicians' prescribing patterns, research indicates that in-person education efforts (sometimes referred to as academic detailing) result in significant improvements. Such interventions appear much more effective than mail education programs or peer review inquiry strategies.

  - When pharmacists are provided with information tools to review drug regimens and when they conduct consultations and counseling with physicians and patients, utilization problems can be significantly reduced. Patient counseling can be improved through training pharmacists in communication skills.

  - A number of education strategies for patients have resulted in improvements on rates of compliance. Improved labelling techniques, use of reminder aids and in-home counseling by pharmacists are some of the strategies that have proven successful.

RECOMMENDATIONS

- The HCFA should plan for the phasing in of a comprehensive Medicare DUR program designed to promote quality of care, control program costs and ensure program integrity. The DUR process should encompass all beneficiaries, notwithstanding deductible status.

- The program should incorporate review and education functions at three levels of the drug therapy process. As soon as is feasible, the program should include the following elements at each level:

Pharmacist Level

- The electronic claims processing (ECP) data base and system should enable the pharmacist to record all drug transactions for all beneficiaries, verify a patient's eligibility and deductible status, and be alerted by computer prompts to potential mismedication errors. Consistent with the stipulation in the Conference Report that requires all participating pharmacies to "review the medication profile of all beneficiaries...before filling prescriptions," the ECP system should also provide pharmacists with a full screen display of the patient's drug regimen.

- The ECP system should be compatible with those used for Medicaid claims processing.

- Participating pharmacists should be required to review all Medicare beneficiaries' drug regimens and assure that in accord with carefully developed criteria all Medicare patients have access to counseling services regarding appropriate administration of the drug, potential side effects and related therapeutic issues. When a potential adverse reaction exists, pharmacists should consult with physicians and patients before dispensing the drug.

Drug Bill Processor/Claims Processing Level

The drug bill processor should:

- Utilize prepayment edits to identify cases of duplicate and erroneous billing, and perform other program integrity audit functions on a retrospective basis to identify cases of fraud and abuse.

- Evaluate the quality of information supplied by the drug bill processor to pharmacists and assess the range and nature of use of that information by pharmacists.

- Conduct some automated therapeutic review.

Post Payment Level

- Using claims data collected at the drug bill processor level, a review of prescribing and utilization behavior should be conducted to identify physicians, pharmacists and patients who demonstrate patterns of mismedication and to target high risk segments of those groups for education efforts.

- Education efforts for those target groups should be implemented at the local level and outcomes from such interventions should be monitored and evaluated for effectiveness.

- The Health Care Financing Administration (HCFA) and the Public Health Service (PHS), individually and collaboratively, should promote improvements in the prescribing, dispensing, and utilization of drugs for older adults by taking the following actions:

  - Make funding available to finance research and demonstration projects that will test DUR interventions and evaluate their relative benefits and cost.

  - Establish a blue ribbon panel to develop DUR criteria that will serve as a national standard for DUR programs conducted throughout the country; to make specific recommendations regarding expansion of curricula in U.S. medical schools in the areas of pharmacology and geriatrics; and to make additional policy recommendations, as needed, in regard to improving drug utilization among the elderly.

  - Expedite issuance of FDA guidelines to manufacturers to ensure adequate testing of drugs on elderly populations.

ADDITIONAL STUDIES

- The OIG is conducting a number of additional studies related to Medicare DUR. They cover the following topics: the disciplinary practices of State pharmacy boards, the clinical role of the community pharmacist, the privacy implications of the Medicare prescription drug benefit's electronic claims processing system, the enforcement of drug regulations, the medication regimens of older adults, and the technical implementation issues associated with the Medicare prescription drug benefit.

COMMENTS

The American Medical Association, the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, the Public Citizen Health Research Group, and the Public Health Service expressed considerable support for our recommendations. The Health Care Financing Administration, the National Association of Chain Drug Stores, and the Pharmaceutical Manufacturers Association expressed support for the concept of drug utilization review, but raised a number of concerns about our recommendations. Their comments and our response to them are presented in general in the final section of the main body of the report and in detail in appendix I.

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INTRODUCTION

In June 1988, Congress passed the Medicare Catastrophic Coverage Act. In anticipation that the final act would include a prescription drug benefit for Medicare beneficiaries as well as a requirement that the Secretary establish a companion Drug Utilization Review (DUR) program, OIG had initiated a study in February 1988 to identify the major policy and program issues relevant to development of a Medicare DUR strategy.

The Act's major provisions related to coverage of prescription drugs include the following:

- Effective January 1991, enrollees in Medicare Part B who have exceeded a deductible threshold of $600 in a single year will be eligible for partial coverage of costs of outpatient prescription drugs (as defined in the Act). Copayment by the patient will be 50 percent in 1991, 40 percent in 1992, and 20 percent in 1993 and thereafter. Further, the deductible threshold will be adjusted each year to ensure that no more than 16.8 percent of Medicare beneficiaries will be eligible for the benefit.

- With certain narrow exceptions, use of a formulary is prohibited.

- Coverage will not include drugs dispensed in a quantity exceeding a 30-day supply. The Secretary may authorize up to 90 days in special circumstances.

- The Secretary is authorized to contract with "limited carriers," i.e., drug bill processors for operation of an electronic point-of-sale claims processing system and is to provide participating pharmacies with equipment and technical assistance necessary to participate in the claims processing system. The system will provide a data base for tracking beneficiary drug transactions, monitoring eligibility, and documenting deductible status.

- The Secretary is required to establish a DUR program to identify patterns of inappropriate prescribing and dispensing practices, and instances of substandard care and potential adverse drug reactions. Additionally, the Secretary must establish an educational program to educate physicians and pharmacists about quality of care issues.

For purposes of this inspection, we used the DUR definition and program objectives as developed by Dr. T. Donald Rucker and recommended by the American Medical Association:

"DUR is a formal program for assessing data on drug use against explicit, prospective standards, and, as necessary, introducing remedial strategies to achieve some desired end. The three primary objectives are (1) improvement in the quality of care; (2) conserving program funds and individual expenditures; and (3) maintaining program integrity, i.e., controlling problems of fraud and benefit abuse."

The focus on improvement in quality of care as well as program integrity issues was considered integral to the inspection strategy for two reasons. First, in deliberating on the bill, the Congress held a number of hearings related to problem of mismedication among the elderly and the implications of such problems for development of a DUR program. As a result of those hearings, specific language was included in the Act that requires the Secretary to establish a program geared to improving the quality of drug therapy for the elderly. Second, in the course of reviewing the relevant drug utilization research, the inspection team concluded that significant economic savings would be gained by including a quality of care dimension to a Medicare DUR program, and that, in fact, those potential savings may well exceed savings related to program integrity issues.

Data were gathered for the inspection from three major sources:

- A survey of 48 State agencies that had been providing prescription drug benefits to Medicaid patients and operating their own DUR programs, as well as an additional 6 State agencies that provide similar benefits through programs designed specifically for the elderly.
- Alternative review of relevant research findings related to drug utilization among the elderly, including topics such as overall utilization patterns, problems of mismedication, and experimental interventions to improve drug use.
- A series of interviews with researchers, academics, and practitioners in the fields of geriatrics and pharmacology; former and current policy makers at the State and Federal levels; congressional staff involved in drafting of the Act; and private sector pharmaceutical providers.

The findings from these data gathering efforts have been incorporated in this report which attempts to describe the widespread pattern of mismedication among older adults, identify those aspects of the drug therapy delivery system that have created the problem, and describe DUR interventions that appear most promising.

The mismedication of the elderly is an issue that transcends the new Medicare prescription drug benefit. It does, however, have a number of important implications for design and management of a DUR program. With implementation of the Act, HCFA policy makers will be presented with a unique opportunity to have major impact on a widespread health problem among the elderly. The HCFA is now preparing a request-for-proposal for the electronic claims processing system that will be the infrastructure for operating the benefit program. Equally important, that system will serve as the data base for all DUR activities. As one expert in the field has described it, the system will be an intersection for clinical practice, epidemiology, and computer technology. Because of the unique importance of the claims system in the overall operation of the program, we have made a number of recommendations regarding basic system requirements. On a broader level, we have also included specific recommendations to HCFA and PHS that are geared to resolving some of the structural weaknesses in the overall drug therapy delivery system.

FINDINGS

MISMEDICATION AMONG OLDER ADULTS

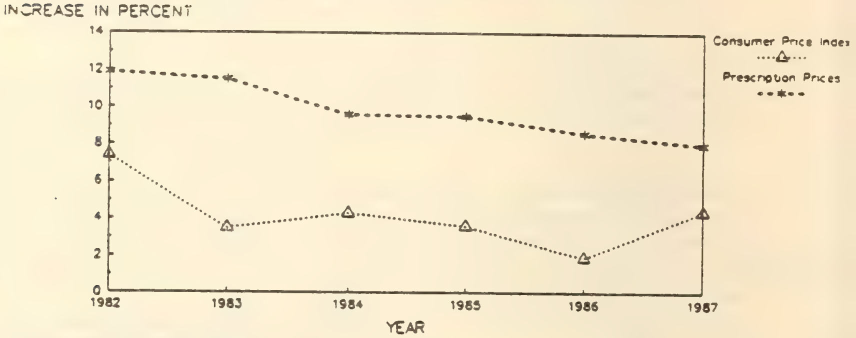
There Is A Widespread Problem Of Mismedication Among Older Adults. The Problem Is Likely To Grow When The Medicare Drug Benefit Is Implemented, Unless An Effective DUR Program Is Developed.

There are serious cost and quality of care risks associated with implementation of the new prescription drug benefit within the Medicare program. Anecdotal evidence from State pharmaceutical assistance programs for the elderly and independent research in the field of geriatric pharmacology indicate that, unless an effective drug utilization review program is instituted by HCFA, existing problems of excessive and inappropriate prescribing for the elderly will be further exacerbated by the new benefit.

In order to assess the potential risks associated with the prescription drug benefit, it is useful to review recent consumption and cost trends among the general population as well as within the subset of the elderly. For the entire U.S. population, the total number of prescriptions filled between 1976 and 1986 rose by 6.6 percent, while the number of pills per prescription increased by 14 percent over the same period.[1] At the same time, prescription drug prices have increased substantially and at a much higher rate than inflation[2] (figure 1).

FIGURE 1

INCREASE IN PRESCRIPTION DRUG PRICES VS. CONSUMER PRICE INDEX, 1982 - 1987.



Source: AARP Issue Brief, March 1987;
Testimony before Senate Subcommittee on Aging,
July 20, 1987.

Price increases and growth in consumption are reflected in the remarkable increase in total retail prescription drug sales between 1974 and 1986 from $5.7 billion to $18.9 billion, a 226 percent jump.[3]

Within the elderly population, utilization rates and costs are particularly high. Although Americans who are 65 years or over constitute only 12 percent of the population, they use over 30 percent of the prescription drugs and 40 percent of the nonprescription drugs dispensed.[4] Another measure of consumption by the elderly is that in 1986, a total of 613 million prescriptions were filled at retail drugstores for older adults, an average of 15.5 prescriptions per person.[5] The incidence of polypharmacy (the use of multiple drugs at one time) is also especially high among older adults. Sixty-one percent of the institutionalized elderly receive three or more different prescription drugs in a year; 37 percent receive five or more; and 19 percent seven or more.[6]

One of the primary reasons for this high level of use is that the elderly are more likely to have chronic diseases. Eighty percent of those over 65 have one or more chronic illnesses,[7] and across the entire elderly population, there is an average rate of three to five chronic diseases per non-institutionalized patient.[8] In terms of drug costs, the elderly have been particularly hard hit by the rising prices of prescription drugs, given the fact that cardiovascular, antihyper3tensive, and non-steroidal anti-inflammatory medications most often prescribed for the elderly are among the most expensive types of drugs.[9]

There is little question that drug therapy is an essential component of long-term health care for the elderly. Reductions in deaths from heart disease and strokes can be attributed in part to development and use of cardiovascular and anti-hypertension drugs. Effective outpatient drug regimens have also permitted the elderly to maintain independent living status and to improve the quality of their lives.[10]

Despite the obvious benefits, however, there are profound risks associated with use of prescription drugs, particularly among the older adult population. A growing body of evidence accumulated over the past 10 years indicates that mismedication of the elderly has become a critical health care issue. It has been labeled by some, including the National Council for Patient Information and Education, as the "nation's other drug problem."[11] The issue has become a subject of concern among researchers, practitioners, and policy makers at the national and international levels. Dr. Ira Bennett, editor of the Harvard Medical School Health Letter, has reported that "research shows overmedication and adverse reactions to drugs are prevalent and have probably become epidemic among the elderly."[12]

Mismedication can occur in at least four ways: (1) higher doses are prescribed in cases when a lower dose would provide the same benefits with lower risks; (2) drugs with a greater potential for adverse reactions are prescribed when a less dangerous drug would be just as effective; (3) the particular drug prescribed is unnecessary either because the patient's condition has been misdiagnosed or because nondrug therapy could be substituted; and (4) the combination of the prescribed drug with other drugs in the patient's regimen produces adverse effects.

There are many medical and social reasons that the elderly are more likely to be victims of mismedication; however, there are a few particularly important ones. The first is that there is a higher risk of adverse drug reactions (ADRs) as the number of different drugs taken increases;[13] consequently, the elderly, who use significantly more types and total amounts of drugs than the rest of the population, are especially vulnerable. Because they suffer from multiple chronic diseases, older adults are frequently under the care of more than one physician who may prescribe drugs without knowledge of the patient's full drug regimen. Thus, the physician may be unaware of the potential for drug interactions. Furthermore, as the drug regimen becomes more complicated, there is a greater likelihood that the patient will make an unintentional error.

Secondly, unique physiological changes associated with aging greatly affect the body's metabolism of drugs, thereby increasing the possibility that an appropriate dosage for a younger patient is not appropriate for an older one. Some physicians may not account for these changes when developing a drug therapy program for an elderly patient. "The risk of an adverse reaction is about 33 percent higher in people aged 50 to 59 than it is in people aged 40 to 49, increasing to two to three times higher when people are older."[14]

Identifying and treating cases of ADRs in the elderly can be problematic since symptoms of such reactions are often similar to those typically associated with the aging process and to symptoms of diseases common among the elderly. Further, the effects of mismedication may range from mild, temporary symptoms to serious illness and death.

Because ADRs are frequently misdiagnosed, it is difficult to determine with precision the full scope of associated illnesses, injuries, and deaths. However, severe effects of ADRs have been documented. An OIG analysis of Medicare hospital bills indicates that:

- In 1987, an estimated 200,000 older adults were hospitalized due to ADRs or experienced an ADR while hospitalized.

Other studies have found that:

- Each year, 32,000 elderly adults incur hip fractures due to drug-induced falls.

- 63,000 older adults experience serious mental impairment either caused or worsened by drugs.

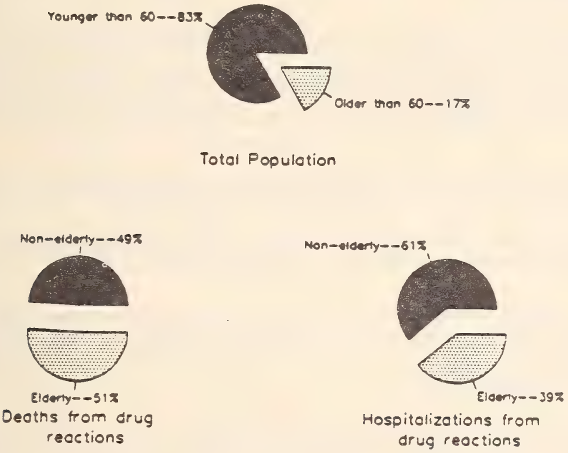
- 61,000 older adults have developed symptoms that mimic Parkinson's disease due to prescribing of anti-psychotic drugs.

- Two million of the elderly are addicted or at risk of addiction to minor tranquilizers or sleeping pills because of using them daily for at least 1 year.[15]

In proportion to the general population, the elderly are considerably overrepresented in terms of hospitalizations and deaths as a result of adverse drug reactions:[16]

FIGURE 2

DEATHS AND HOSPITALIZATIONS AMONG OLDER AMERICANS AS A RESULT OF ADVERSE DRUG REACTIONS



Total Population

Deaths from drug reactions

Hospitalizations from drug reactions

Source: Senate Special Committee on Aging.

Beyond the human costs associated with mismedication among the elderly, there are significant financial costs borne by patients, families, and public and private health insurers. One study conducted by Pennsylvania Blue Shield estimated that the annual cost of drug related hospital admissions of the elderly, along with their subsequent treatment, was $4.5 billion in 1983.[17] (That estimate does not include costs associated with ADRs among the elderly who required treatment other than hospitalization.) Other estimates of health care costs associated with ADRs among the elderly are as high as $7 billion per year.[18]

It is a basic microeconomic principle that price subsidies such as the new Medicare prescription drug benefit will increase both the consumption and, ultimately, the price of a good. The experience of the State of Pennsylvania in implementing its own drug benefit program (PACE), which subsidizes prescription drugs for the elderly, is illustrative. In 1985, at the end of its first program year, PACE beneficiaries were submitting an average of 18 prescriptions per year at a program cost of $62 million. (This consumption rate was significantly higher than that for the U.S. population as a whole.) As would be expected with a new entitlement, the program has grown substantially each year as the number of eligible beneficiaries, the number of prescriptions filled per beneficiary, and the average cost of each prescription have all increased steadily. The most recent projections for the current program year are that average number of prescriptions per enrollee will be 26 per year and total PACE program costs will exceed $180 million.[19] (This represents a 44 percent increase in the average number of prescriptions and a 190 percent increase in program costs in just 4 years.) PACE program staff have also estimated that over 30 percent of PACE beneficiaries are on potentially conflicting drug regimens.[20] The magnitude of such potential conflicts varies among individuals.

The major risks associated with implementation of the new Medicare benefit are, therefore, two-fold: (1) subsidized prices may result in an increase in consumption, thereby exacerbating the quality of care problems of mismedication and overdrugging that already exist, and (2) as consumption increases, health care costs associated with ADR-related illnesses and hospitalizations and with the price of prescription drugs may accelerate.

WEAKNESSES IN THE DRUG THERAPY DELIVERY SYSTEM

The Widespread Problem Of Mismedication Among The Elderly Reflects A Series Of Systemic Weaknesses Throughout The Drug Therapy Delivery System.

The problem of widespread mismedication of the elderly is not the result of fraud, abuse, or malfeasance within the health care system. As one leading researcher in the field has described it: "There is no malevolent force in all of this. What we are fighting here is sheer ignorance and lethargy."[21]

A review of the entire process of administering drug therapy to the elderly reveals a series of fundamental weaknesses throughout the system, beginning at the manufacturer level and extending to the patient's management of his/her own drug regimen.

Manufacturer Level

Systemic weaknesses in the delivery of drug therapy for older adults begins at the pharmaceutical manufacturer level. In the past, drug companies often performed clinical studies required to secure FDA approval on healthy younger adults even though the product may ultimately be approved and marketed for a condition that is common among the elderly. As one noted pharmacology expert described the situation, "We test drugs on young people for 3 months; we give them to old people for 15 years."[22] The FDA has been working with the industry to correct this problem, and indicates that in recent years much progress has been made in including older patients in clinical studies of new drugs.

For the past 5 years, the FDA has been developing and promulgating guidelines for the drug industry that would require inclusion of the elderly in premarketing clinical tests. In 1983, FDA began circulating a discussion paper on the subject. In 1986, the agency released a draft of guidelines for review by the drug companies. In 1988, PHS issued in final "Guideline for Clinical and Statistical Sections of an Application." This guideline goes beyond the issue of whether or not the elderly are included in clinical trials and emphasizes the need for analyzing the influence of variables such as age on the results of these trials.

Also pertinent in this context is the extent to which manufactures provide labeling information on drugs commonly used by the elderly. The FDA reports that in a recent internal survey it concluded 212 of the 425 individual drugs used most often by the elderly contain geriatric information, and that 10 of the top 24 used by the elderly provide such information.[23] The FDA also reports that is has conducted a similar survey of all drugs approved in 1988 and will be providing the results as soon as possible.

As mentioned previously, physiological changes that occur as the body ages create particular sensitivities to drug usage.[24] Some of the changes that affect older peoples' reaction to drugs include:

- Body size and composition: after age 60 body weight decreases and the proportion of body fat increases. Drugs that concentrate in fat tissue will therefore remain in an older person's body for a longer time. Further, dosages appropriate for a younger adult may be too high for an older person whose body weight is lower.

- Liver functions: as adults grow older, the liver becomes less efficient thereby making it more difficult for drugs to be excreted from the body.

- Kidney functions: the filtering ability of the kidneys decreases by 30 percent by the time a person reaches 65 years and continues to decrease steadily thereon. This decreased kidney function can cause certain drugs to accumulate in an older person's body at higher levels and for longer periods of time than in younger people.[25]

It is important to recognize that these age-related changes in body size and composition, liver functions, and kidney functions are subject to wide variations, with some individuals showing significantly less change than might be expected for the population as a whole.

Failure to conduct thorough clinical drug tests on older adults can therefore result in a vacuum of knowledge about appropriate dosage levels and ADR risks. To further exacerbate the problem, the types of medications consumed by the elderly are often inherently more toxic.[26] One of the major risks that is run "by underrepresenting or ignoring the elderly in this important (clinical testing) process is the repeating of disasters such as that of Oraflex in which widespread use of the drug by elderly patients once it was marketed resulted in high rates of side effects and even mortality before the manufacturer voluntarily withdrew it from the market."[27]

The Public Citizen Health Research Group recently conducted a review of the 287 most commonly prescribed drugs for non-hospitalized older adults, and compiled its recommendations for a consumer publication titled *WORST PILLS BEST PILLS*. Among the findings are the following:

- The Group designated 104 of the 287 most commonly prescribed drugs (excluding drugs for treatment of cancer) as medications that should not be used by older adults because safer alternatives are available.
- 20 of the drugs not recommended for use account for more than 83 million prescriptions filled for the elderly each year, at a cost of over $1 billion annually.[28]
- The entire list of 104 drugs in the "do not use" category represents 136 million prescriptions per year, or nearly 25 percent of the total number of prescriptions filled for the elderly each year.

Although reports such as Public Citizen's are useful in sensitizing older adults and health care professionals to the dangers of mismedication, they cannot substitute for a formal set of guidelines that will ensure improved testing and labeling of medications for the elderly.

Physician Level

It is frequently assumed that in treating the elderly, physicians make diagnostic evaluations and prescribing decisions based on the most up-to-date medical information available. A mounting body of evidence, however, suggests that this is frequently not the case and that suboptimal prescribing patterns for the elderly are common: "drugs that are largely ineffective are widely used, dosages or combinations are often pharmacologically irrational, useful drugs are passed over in favor of newer agents that are no more effective but may be considerably more expensive."[29]

Nowhere is it suggested that poor prescribing patterns for the elderly are a product of lack of concern or general incompetence on the part of physicians. Rather, inappropriate administration of drug therapy is, for the most part, a reflection of a serious lack of training for many physicians in the fields of geriatrics and pharmacology.

In 1988, less than 2 percent of the students enrolled in the nation's 127 medical schools were required to take courses in geriatrics. This, however, is an improvement over the past decade. In the mid-1970s almost no geriatrics courses were offered in medical schools.[30] One study published in 1986 reported that medical schools today have only 10 percent of the faculty needed to teach and conduct research in geriatrics.[31] Further, only 1 percent of the continuing education courses for physicians are in the field of geriatrics.[32]

Despite the fact that the elderly population will continue to grow at a steady pace as the "baby boom bulge" ages, the most optimistic estimates are that by the year 2000 the United States will have between 900 and 1600 educators and only 8000 doctors trained in geriatric specialties.[33] (This compares to 479,000 physicians in the United States today.)

The lack of formal training for physicians in the field of pharmacology is equally striking. The problem is compounded by the introduction of hundreds of new medications to the market each year. A 1988 study published in the *Annals of Internal Medicine* reported the following:

- Most physicians receive only one course in pharmacology during medical school.
- By the time a physician completes residency, 100 new drugs have joined the market.
- Nearly every prescription written in 1988 by physicians who graduated from medical school in 1960 is for drugs about which those physicians have received no formal education.[34]

Studies measuring physicians' knowledge of prescribing reflect this educational gap, particularly with respect to psychotropic drugs.[35,36,37] One of the most recent and significant studies was conducted in 1985 and focused specifically on the prescribing knowledge of physicians who treat the elderly. Researchers at Temple University Medical School administered a questionnaire on knowledge of prescribing for elderly adults to a stratified random sample of physicians who treat Medicare patients. Over 70 percent of the respondents failed to pass the exam.[38]

In the absence of adequate education and training in geriatrics and pharmacology, physicians frequently rely on generalized stereotypes about the aging process, and, in selecting a articular drug regimen, they often depend on the promotional materials provided by drug manufacturers. "Many health professionals have a mistaken attitude about the elderly patient that perpetuates...'an unfair elderly stereotype. This stereotype of confusion, lethargy, and weakness, forgetfulness and tremor...unfairly discriminates against the majority of elderly individuals who manifest none of these characteristics. Since the most common manifestations of (ADRs) in the elderly are precisely the same symptoms of this unfair stereotype, professionals who believe that aging is synonymous with deterioration of physical and mental function often overlook medications as the cause of their patients' deterioration."[39] The result of this stereotype can be an "illness-medication spiral," [40] in which ADRs are diagnosed as new illnesses, leading to the prescribing of more and more drugs to treat symptoms and toxicities caused by inappropriate drug therapy. The consequences of such an illness-medication spiral can be as serious as permanent incapacitation and even death of the patient. In its hearings on adverse drug reactions among the elderly, the Senate Special Committee on Aging heard testimony from a number of witnesses whose family members have been tragic victims of this syndrome. [41,42]

In surveys that have asked physicians about the information sources on which they are most reliant in making prescribing decisions, scientific literature is nearly always accorded a more prominent position than commercial sources. However, in studies that do not rely on self-reports, findings indicate that commercial sources of information are relied on far more heavily than scientific literature. One project conducted by Harvard Medical School researchers studied a random sample of physicians in greater Boston and focused on two index drugs whose effects have been shown in published clinical studies to be minimal or not significantly different from those of over the counter drugs, but which are heavily advertised as being effective. The study found that "although the vast majority of practitioners perceived themselves as paying little attention to drug advertising and detail men, as compared with papers in the scientific literature, their beliefs about the index drugs revealed quite the opposite pattern of influence in large segments of the sample."[43]

Findings such as these are not surprising when one considers the resources and technologies used by drug manufacturers to promote their product. Last year, drug companies spent $2.5 billion on promotional activities of their products to physicians·[44] An average of $5,000 per physician is spent each year by drug manufacturers whose promotional activities range from provocative and elaborate print materials to face-to-face visits with physicians.[45] The issue is not one of deception, but rather of aggressive and sophisticated marketing techniques that are designed to sell the maximum volume of drug products. The sales staff are typically not formally educated in pharmacology; in 1988 less than 5 percent of the detail men promoting drug sales had formal pharmacology training.[46] Evidence, however, indicates that these detail men and their supporting print materials are the primary source of drug information for many physicians.

Community Pharmacy Level

Within the health care delivery system, pharmacists are seen as providers of a unique service, that of "disseminating information concerning all aspects of medication (to both) health professionals and the general public." [47] Pharmacists' professional associations have, as one of their standards of conduct, the requirement to consult with physicians and counsel patients on administration of drug therapy and in sixteen States, boards of pharmacy have instituted mandatory patient counseling regulations.[48] Thus, in theory, the community pharmacists should serve as a quality control mechanism to identify cases of mismedication.

As indicated in a number of surveys, community pharmacists see themselves as willing and able to provide counseling services to patients and believe that they do, in fact, provide such services on a regular basis.[49] However, a number of observational studies indicate that this may not be the case. Much of the literature emanating from these studies has been "critical of pharmacists in terms of the small percentage of patients who receive any consultation, the brevity of the consultations that do take place and the inadequacy and inappropriateness of the pharmacists' decisions in regard to patient care."[50]

Reports on the rate of verbal counseling provided by pharmacists have been as low as 30 percent for all patients served, and when dispensing refills, that rate is even lower.[51] Further, when filling a new prescription the average length of time spent in consultations during routine provisions of services has been found to be only 20-30 seconds.[52,53] "One pioneering observational study of pharmacists indicated that (they) devote little of their work time to patient communication and half of the time they do spend talking with patients is on non-professional communication."[54]

Even when patient counseling is mandated by State board regulations the performance of pharmacists can remain unchanged. A study conducted in Kansas evaluated the effects of mandatory patient counseling regulations 2 years after they were implemented and found that the new requirement had no effect on the amount or quality of counseling provided by pharmacists. Among other findings of that study were:

- There was a significant increase in the number of pharmacists using auxiliary labels to supplement verbal instruction.
- The majority (53 percent) who did use labels used them as the only means of supplying patient information.
- A much higher percentage of chain pharmacists used auxiliary labels with no verbal counseling.
- In 38 percent of the pharmacies, non-professional staff gave the prescription to the patient "thus performing, unsupervised, the final and virtually most important step in the process....that of counseling the patient in proper self medication."[55]

In terms of community pharmacy services for the elderly, who typically have more complex drug regimens and are likely to be treated by more physicians than younger patients, the consulting role of the pharmacist is particulary important. However, studies show that the elderly fare poorly in this regard. Over 70 percent of all patients report receiving no information from pharmacists[56,57] and for elderly patients the incidence is even higher than for younger adults.[58]

The community pharmacy profession is in a state of flux at the present time, complicated by the fact that its traditional market has become considerably more competitive. "Expansion of hospitals with ambulatory care, mail order and deep-discount prescription services, and physician dispensing..."are just a few of the market challenges facing community pharmacies.[59] One response to these market challenges has been the new technology introduced to improve productivity and enhance competitiveness. Pharmacy robots capable of "reading" and filling prescriptions are being used in Japan and are being tested in the United States.[60] Although quality of service to the patient is seen as a useful marketing technique, technological and market forces have combined to "depersonalize" the services offered by community pharmacies to patients.

Patient Level

Notwithstanding the systemic flaws at the manufacturer, physician, and pharmacist levels, drug utilization problems can and often do occur at the patient level in administration of drug therapy. Noncompliance, or medication behavior problems of patients, include underuse and overuse of a drug, as well as items such as sharing of drugs among family and friends, use of outdated prescriptions, and use of medications that have been damaged due to poor storage.

A review of the literature concerning compliance with prescription drug regimens indicates that older adults' compliance rates range from 38 percent to 57 percent, with an average rate of approximately 45 percent.[61] Some research indicates that "compliance is relatively good among children, poor among adolescents, good during middle years, and, again, relatively poor with advancing age."[62]

Advanced age is not in itself a reliable predictor of non-adherence.[63] However, studies indicate that use of multiple medications,[64] duration of drug therapy,[65] and living status[66] (i.e., living alone rather than with family or friends) are all variables that negatively affect a patient's compliance with drug therapy. Because older adults are more likely to suffer from chronic diseases and to take more types and amounts of drugs, they may be particularly prone to medication behavior problems. Compounding the problem is the fact that adults' vision tends to deteriorate over time, making it difficult for some elderly patients to read and understand instructions on labels.[67]

As mentioned previously, older adults consume nearly 40 percent of all over-the-counter (OTC) drugs, a practice that complicates prescription drug regimens for some elderly patients. With the increasing number of very potent drugs being reclassified for OTC use, self-prescribing becomes more risky, especially among older patients who may already have a complex prescription drug regimen. Patients who are self-administering OTC drugs may not communicate that fact to physicians and pharmacists who could identify potential drug interactions and other hazards.

Thus, even when the appropriate drug regimen is prescribed and dispensed, breakdowns can occur at the patient level. Although compliance problems are the product of a multitude of variables, all of which can never be resolved, evidence suggests that the development of a DUR program for Medicare beneficiaries should be focused to some degree on this critical stage of drug therapy.

STATE SURVEY RESULTS

From A Quality Of Care Perspective, State Medicaid Dur Policies And Program Functions Have Limited Applicability For A Medicare Prescription Drug Program.

Our survey of the 48 State Medicaid agencies found that most DUR programs are geared to identify and correct problems of program integrity, rather than quality of care.[68] Given this policy focus and the fact that Medicaid populations differ significantly from Medicare populations, both in demographic profiles and in drug consumption patterns, the Medicaid DUR efforts alone should not be used as a model for developing a Medicare DUR program.

In general, State Medicaid agencies define the DUR problem as one of abuse by individual recipients, and, to a lesser degree, fraudulent billing practices by pharmacists and physicians. An overwhelming majority of survey respondents reported that drug utilization cases in the State Medicaid programs involve narcotics and controlled substances. Forty-two (88 percent) of the States reported that DUR cases involved certain types of drugs and nearly 80 percent cited narcotics and other drugs with street values as the specific drugs involved.

Because of the manner in which State Medicaid agencies have defined the drug utilization problem, resources have been allocated and monitoring devices selected to identify patients who abuse the system, either because of addiction problems or because of involvement in illegal sale activities. Program functions have also extended to monitoring pharmacists and physicians who may be involved in fraudulent or abusive activities.

Although we found that the majority of States (69 percent) use some form of prepayment method to identify utilization problems, those functions are almost exclusively geared to identify administrative problems or to enforce eligibility restrictions. The nature of prepayment review methods for the 33 States that use them are as follows:

- Five States require preauthorization to increase supply limits.

- Ten States require preauthorization for non-formulary drugs.

- Fifteen States perform prepayment edits to enforce lock-ins (requirements that patients suspected of misuse use a single doctor and/or a single pharmacy), to screen for dispensing of non-formulary drugs, or to identify duplicate or faulty billings by pharmacists.

Further, the majority of State agencies (65 percent) reported that they do not encourage pharmacists to review prescriptions prior to dispensing a drug.

It is clear, therefore, that at the prepayment level, Medicaid DUR programs are designed to screen for eligibility, formulary and quantity requirements, and instances of administrative error and abuse. With only one exception, State programs are not designed to flag quality of care problems (e.g., potentially dangerous drug interaction or duplicative therapy) at the point of sale.

In terms of post payment strategies, all States report using some method of profiling to identify utilization problems, but again, these "problems" generally fall into the category of patient, pharmacy, or physician fraud and abuse.

At the post payment level, all of the State agencies surveyed reported using the method of patient profiling to establish a data base for utilization review. A lower proportion of States use pharmacy and physician profiling methods. Ninety percent rated patient profiling as the most effective post payment strategy for identifying program integrity problems. Only five States reported using a peer review committee to review cases of suspected misuse of drugs, and only three States reported that post payment review systems were used to identify contraindicated prescribing patterns.

Another reflection of the State agencies' perspective on the DUR process is seen in the methods most typically used to address utilization problems. Lock-ins were reported by 69 percent of the States as the most frequently used corrective method. Only 33 percent of the agencies reported engaging in educational outreach prior to the onset of problems, and nearly all such outreach efforts consisted of journal articles, seminars, and bulletins. For those States that use educational methods to correct already-identified problems, 33 percent reported that such activities consist only of warning letters sent to one or more of the involved patients.

Despite the fact that Medicaid DUR systems are designed to focus on program integrity rather than quality of care problems, there are indications that State officials are aware that quality issues are deserving of more attention. Although significantly more prevalent among older adults, problems of mismedication unrelated to fraud and abuse are not confined to the elderly population and this fact has been recognized by State Medicaid agencies.

In terms of expanding their program scope to identify and include quality of care issues, some States face a number of constraints. Inadequate resources in terms of financing, staffing, computer software, and data gathering capabilities were cited as a significant impediment to program expansion. Further, some DUR program officials reported that State level regulations limited their authority to narrow program integrity review and enforcement.

Agency staff's responses to questions about their own future directions and about advice to Medicare administrators reflect a broader perspective than their own current practices suggest. When asked which approaches have the most potential for addressing utilization problems in the future, education (31 percent) and establishment of peer review committees (31 percent) were mentioned most frequently. Further, when respondents were asked to identify the most significant initiatives Medicare administrators should take in designing a DUR program, the following items were mentioned most frequently:

- Implement education programs (33 percent).

- Use sophisticated data collection techniques and software to identify utilization problems (29 percent).

In summary, the OIG State survey's most significant finding may be that in designing a national DUR program, Medicare administrators should do what the States say rather than what they do. Although some States have instituted practices to address quality of care problems, the survey findings indicate that more common State practice is not particularly relevant to a Medicare DUR program.

OTHER DUR INTERVENTIONS

The Results Of DUR Interventions Instituted By Some State Level Programs And By Researchers And Practitioners Are Relevant To The Design Of A Medicare DUR Program.

Although, as a rule, most State Medicaid DUR practices are confined to program integrity issues, some State level Medicaid and pharmaceutical assistance programs have implemented efforts to identify and correct quality of care problems. Further, independent research and experimental education programs have also produced results that are instructive for Medicare. Some State Medicaid programs and pharmaceutical assistance programs for the elderly have instituted interventions focused on quality of care issues. One of the most sophisticated designs for such a program is that of the Minnesota Medicaid Agency. The major procedural components of the Minnesota program are as follows:

- A panel of medical experts develops a list of therapeutic criteria that identifies high risk drugs, drug use characteristics, and disease classifications that present the greatest potential for mismedication problems.

- The State agency contracts with a provider who uses the preselected therapeutic criteria to review Medicaid computer tapes of drug purchases and identify "exceptional drug profiles" of patients that appear potentially hazardous. These reviews are computer-generated and use algorithms to sort information so that high risk patient profiles can be flagged.

- The drug history profiles are then transmitted back to the State agency which uses DUR peer review committees of health care professionals to conduct a case by case review. Such a review attempts to isolate cases of suspected overutilization and underutilization, adverse drug interactions, and contraindicated drug therapy.

- The DUR committee sends written inquiries to the practitioners associated with the questionable therapy and evaluates each response to determine whether the information provided by the practitioners justifies the drug therapy in question or whether further remedial action (e.g., continued monitoring, referral to local providers' professional society, referral to State boards of medicine and pharmacy) should be taken.[69]

The model described above includes elements that appear to have potential applicability for a Medicare DUR program. First, the development of therapeutic criteria as an underlying construct for the entire review process is seen as a valuable tool with which to screen large amounts of drug utilization data.

There may also be a value to developing additional criteria with more elaborate screens at the DUR committee case review level, as other research indicates. In a study conducted by Michael Smyer, et al., for the Pennsylvania PACE Program, members of multiple peer review committees within the State were surveyed and asked to rate specific drug interactions in terms of their clinical significance for elderly patients. Such ratings were then compared with scientifically based authoritative standards. "The most striking finding was a very high variability among DUR members (in terms of their ratings). Limited consensus was achieved for only a few types of interactions."[70] This suggests the need to develop a second level of more sophisticated screens/criteria at the committee review level to ensure that such reviews are consistently focused on the highest risk groups.

The value of developing a thorough drug utilization data base with which to conduct vital computer-generated screens is also instructive for Medicare DUR program planners. The volume of drug transactions projected for Medicare beneficiaries (700 million annually) will require the maximum amount of automated review that is feasible. According to experts, one crucial element that should be included in such a data base is a physician provider's identification number.[71] The absence of such a standardized national identification system would obviously limit the ability of DUR reviewers to institute remedial action.

There has been some discussion among congressional and HCFA staff about the advisability of matching diagnostic codes with prescriptions. Although the legislation does not require that diagnostic information be provided by the physician with the prescription, there is some interest in developing a DUR data base that would match Medicare part A and B claims data (which include a diagnostic code) with DUR patient profiles in order to expand the patient information available for DUR review. Findings indicate, however, that use of standard diagnostic codes would have limited utility for a Medicare DUR program. Researchers who have used Medicaid data bases (which include diagnostic codes) for DUR-related research report that there are a multitude of problems associated with use of such codes in making clinical judgments.[72]

First, there are several problems related to the accuracy and intelligence of diagnostic code data. For Medicare, part B procedure codes are frequently listed as "doctor's office visit", which provides no information about the patient's condition. Further, patients themselves sometimes complete part B claim forms, a practice that further exacerbates the accuracy problem. It is routine in some office practices for clerks who do not have clinical expertise to complete claim forms, and, even when they are completed correctly, computer sorting of information may be flawed. One university-based project that used diagnostic codes to conduct research on ulcer disease was seriously flawed because computers and clerks added trailing zeros to a code, unaware of the fact that such an addition resulted in a miscoding error that changed the diagnosis.

Secondly, even if the accuracy problems could be resolved successfully by improving coding models and training health care personnel, the problem of "paper compliance" would remain. Typically, multiple diagnoses are associated with treatment of the elderly, all of which may be addressed in a single office visit. It is likely that physicians would quickly learn which codes should be associated with particular prescriptions in order to avoid the administrative burden of responding to a DUR-related inquiry. A system of "paper compliance" would then be instituted among physicians treating Medicare patients, thereby adding no useful information for DUR purposes and resulting in no clinical change of behavior among practitioners.

Beyond the issue of the ingredients of a data base, other elements of State level DUR experiences are instructive for Medicare. Like Minnesota, several States have used the peer review committee method to identify quality of care problems, and, although this technique has been found useful in identifying questionable utilization patterns, there are serious questions about its efficacy in correcting such problems. The process itself is lengthy and labor intensive by nature; it can sometimes take 12 to 18 months from the time a drug is prescribed to the point at which a DUR committee sends a written inquiry to the physician. The requirements of assembling computer tapes, conducting automated screens, and completing case by case reviews of questionable profiles precludes timely identification of what could be life threatening instances of mismedication for elderly patients. By the time a physician is notified by a DUR committee that a patient's drug regimen is in question, the patient may have died, the drug regimen may have been adjusted, or the patient may have moved and/or changed physicians.

More importantly, the inquiry process itself has several severe limitations, both in philosophy of approach and effectiveness. Despite attempts to construct written inquiries that avoid offending the physician, the fact that a State authority is requiring a practitioner to justify his actions can carry an implied threat in many physicians' minds. The prospect of a DUR committee referring a physician for punitive action to a licensing board or enforcement agency is obviously not lost on the physician. The enforcement undertone of the entire process is therefore not likely to be perceived as a supportive, educative experience for the physician whose questionable prescribing patterns may be just the result of lack of appropriate information. Additionally, it is typical that DUR committees refer only the most egregious cases for sanction or punitive action. Instances of malpractice that require such enforcement action are difficult to document and prove, even when punitive action is clearly indicated.

In summary on this point, the peer review process, while somewhat useful in identifying potential problems, may not be a particularly effective technique for affecting changes in the behavior of physicians on a broad scale and, except in cases of clear abuse, is highly dependent on the willingness of practitioners to cooperate in what they may perceive to be an unnecessarily threatening process.

In terms of ameliorating patterns of mismedication, a number of initiatives by researchers and practitioners appear promising. Perhaps the most important and effective trial of interventions has been directed at the physicians' level of the drug therapy process.

Traditionally, the use of mailed educational materials has been a favored technique for providing physicians with continuing education services. However, research conducted over the past 5 years has raised serious questions about the efficacy of this method. A study published in the *Journal of the American Medical Association* in 1986 reported results of a mailed continuing education program for primary care physicians concerning management of hypertensive patients. A standardized trial in two urban communities in Canada "demonstrated no influence of a mailed...education program on the practices of physicians or on the control of the blood pressure of hypertension patients referred (by the project staff)."[73]

The pioneering work done by Dr. Jerome Avorn of the Harvard Medical School in measuring the relative effectiveness of various education methods on changing clinical behavior appears particularly relevant for design of a Medicare DUR program. Avorn and associates conducted a randomized controlled trial of 435 physicians in a four State sample. Using Medicaid patient profile tapes, project staff identified physicians who were participants in Medicaid programs and who prescribed high levels of one or more of three groups of target drugs that are questionable in terms of effectiveness or are unnecessarily costly.

A mailed education program was administered to one portion of the sample, using print materials that were commercially designed and fashioned in the style used by drug manufacturers to promote their products. These "unadvertisements" were designed to counter overprescribing of the target drugs by means of attractive, easily read and understood messages. A second segment of the sample were visited by clinical pharmacists trained by project staff in the relevant pharmacological aspects of the target drugs and in communication techniques. These face-to-face contacts were conducted in a positive and supportive manner; physicians were not approached as problem prescribers, but rather, were told that they had been selected as subjects for a university-based drug information program. In addition to receiving the same "unadvertisements" sent to the print-only group, these physicians were visited twice by a clinical pharmacist who reviewed the print materials with them and encouraged them to reduce their prescribing of the target drugs. The third segment of the sample, the control group, was exposed to no intervention. Among the significant findings of this study are the following:

- There was no statistically significant effect of the education intervention on physicians who received the print materials only.
- For physicians who received face to face visits, there was an average reduction of 782 units of the target drugs per physician.
- Ninety-two percent of the group randomly selected for face to face intervention agreed to participate, and many asked for more drug education as a result of the visits.
- A time series analysis indicated that the improvements in prescribing habits remained constant over time, with "no significant diminution of effect 9 months after the start of intervention."

- The rate of prescribing change documented was independent of characteristics of physicians themselves (e.g., age, specialty, size of Medicaid practice, intensity of previous target drug use).[74]

A companion analysis by the study group analyzed the benefit/ cost ratio of the project and indicated that implementation of a personal visit intervention program for 10,000 physicians would lead to projected drug cost savings of $2,050,000 compared to program costs of $940,000. Further, the benefit/cost ratio could be increased to at least 3.0 if higher volume prescribers were targeted. "Net benefits would also increase if non Medicaid savings were added or if the analysis included quality of care considerations."[75]

Dr. Wayne Ray of Vanderbilt University has also conducted research on the effectiveness of physician education programs among Medicaid prescribers in Tennessee. As was the case in Avorn's research, mailed, commercially designed brochures had no effect on physicians' prescribing behavior. In the Ray study, the effectiveness of office visits by pharmacists was also measured against visits by physicians to target practitioners. The physician counselors were found to be even more effective than pharmacists in reducing prescribing of the target drugs.[76]

One particularly significant finding of both Avorn's and Ray's research is that physicians are equally receptive to education about drugs that are effective but unnecessarily costly (i.e., less expensive but equally effective drugs are available), as they are about drugs for which cost is not an issue, but effectiveness is questionable. Although it has been assumed by some researchers that physicians are less concerned with cost issues than with clinical concerns,[77] these studies demonstrate that physicians are willing to substitute more cost effective regimens if the educational approach is made in a positive professional manner.

At the dispensing level, there has been some recognition within the industry that significant value is added to community pharmacy services when pharmacists are given the tools to review a patient's drug regimen at the time of dispensing[78] Several national retail chain corporations have developed a data system that their pharmacists are required to access when filling a prescription.[79] Personal computer screens display a history of prescriptions purchased by the patient at all of the company outlets (including out-of-State transactions) and the computer provides prompts to the pharmacist when a prescription that appears to conflict with the patient's regimen is about to be filled. Thus, the pharmacist has a complete record of the patient's drug regimen to conduct his own analysis and, when necessary, raise questions with the patient and/or physician, and is aided by a pre-programmed warning system that flags potentially dangerous drug combinations. This system is relatively new within the industry but it does demonstrate the feasibility of making automated drug records available to the pharmacist.

Considerable research has also been conducted to identify variables that affect the level of pharmacist consultation with patients. Studies have examined variables including age of the pharmacist, affiliation with chain vs independent pharmacies, and physical setting of the pharmacist's work station.[80,81] Two factors that appear to be reliable indicators are the pharmacist's attitude toward patient consultation [82] and the amount of privacy available to the pharmacist in the setting where consultation occurs.[83] Further, in studies measuring the effects of experimental interventions, it has been shown that patient counseling is improved when pharmacists are taught communication skills.[84]

Researchers in this field and segments within the pharmacy field itself are beginning to recognize the value-added aspect of pharmacist counseling with patients and physicians, particularly within the elderly population.[85] Some privately funded demonstration projects are underway to measure the clinical outcome and cost effectiveness of improving consultation services. The results of these and previous experimental interventions will be useful for Medicare administrators in designing that segment of the national DUR program that should occur at the pharmacist level.

Finally, studies conducted to determine the effectiveness of various patient interventions have also tested the relative value of various instruction and education techniques. In one study of 158 ambulatory patients who were elderly and receiving medication for cardiovascular conditions, the combination of oral instructions and a reminder calendar package was the most successful method for improving compliance behavior. [87] This reminder aid method has also been tested in other studies and found to be effective.[88] Labelling has also been found significant in terms of adhering to a drug regimen. Imprecise instructions (e.g., instructions such as "to be taken as directed"), and instructions that are not printed or typed in large letters have been negatively associated with patient compliance among older adults.[89]

One project conducted by researchers at the University of Washington studied the medication behavior of 183 elderly apartment residents.[90] The patients were provided written instructions and were visited at home by pharmacists who counseled them on compliance with and comprehension of their drug regimens, on potential drug interactions and other ADR's, and on appropriate drug handling and storage. The interventions were applied intermittently for almost two years. One year later, a final assessment indicated that there was a 39 percent decrease in the number of medication behavior problems and that a significant decrease of 11 percent had occurred in the number of prescriptions taken. "These results suggest that pharmacist consultation provides an effective health prevention strategy in elderly residential settings."[91]

The practice of "brown bag" lunches conducted in elderly residential settings, in which residents bring all of their medications to a meeting with a consulting pharmacist has also been recommended by experts as a useful educational technique. [92] The use of a drug worksheet such as that designed by the Public Citizens Health Research Group is another method designed to assist elderly patients in recording significant information about their drug regimens and in presenting such records to physicians and pharmacists.[93]

The cost savings associated with improving patient compliance have been well documented in a number of studies. [94] One project conducted by Joyner, et al., in 1983 was able to accomplish a mean compliance rate of 95 percent, at a cost of $35 per patient for a sample of older adults living in a congregate housing facility. The benefit/cost ratio for the intervention used was estimated in the range of 7.0 to 14.0, depending on the risk level of the population targeted.[95] This and other research leaves little question that improving patient compliance through education yields significant savings in both social and financial costs.

RECOMMENDATIONS

DEVELOPMENT OF THE DUR PROGRAM

- The HCFA should plan for phasing in a comprehensive DUR program designed to promote quality of care, control program costs, and ensure program integrity. The DUR process should encompass all beneficiaries, notwithstanding deductible status.

Discussion:

The HCFA has a formidable task before it just in terms of the technical aspects of implementing the drug benefit. Enrolling participating pharmacies, designing requirements for electronic claims processing, and contracting with providers to operate the claims system are only a few of the major tasks that will need to be completed. Organizational and resource related issues associated with planning and implementing the new system will consume the attention of HCFA staff at the policy and operational levels. However, a critical error will be made (1) if substantial attention is not given to the design and development of a comprehensive DUR program to be implemented, in phases, when the drug benefit becomes effective and (2) if approaches taken in establishing the electronic claims processing system impede the phasing in of the DUR program.

Although precise figures cannot be placed on the costs associated with mismedication and economically inefficient prescribing patterns for the elderly, there is little question that significant savings can be achieved through implementation of a DUR program. (As mentioned previously, some estimates of ADR related treatment costs alone range as high as $7 billion annually.) Such savings will affect expenditures in the Medicare Health and Supplemental Insurance Funds if hospitalizations and treatment related to ADRs can be avoided, and will reduce outlays in the Drug Benefit Fund if cases of overutilization and prescribing of unnecessarily costly medications can be eliminated.

Notwithstanding potential program savings related to DUR, the new prescription drug benefit presents HCFA policy level officials with an opportunity to make a major impact on a widespread health problem among the elder ly. The human costs associated with death, illness, and incapacitation among the elderly as a result of mismedication are incalculable. Establishment of a comprehensive Medicare DUR program that emphasizes therapeutic as well as program integrity issues will afford HCFA a leadership role in resolving this critical public policy problem and may serve as a model for public and private providers of drug benefits.

The DUR process should encompass all beneficiaries, regardless of an individual's deductible status. A number of elements support that policy direction:

- Data on all beneficiaries will be collected in any case so that deductible status can be documented by the claims processing system. Given the tremendous human and program costs associated with mismedication of the elderly, a valuable information resource (i.e., the data base on all drug transactions) would be underutilized if DUR efforts were targeted only for those who have exceeded the deductible limit.

- Even though a beneficiary may never reach the deductible threshold, significant costs for treatment of ADR related illnesses may be incurred by the patient, by Medicare and/or by a supplemental carrier. Further, DUR interventions may actually preclude a beneficiary from reaching the deductible limit if a case of inappropriate utilization can be identified early in the process.

- All Medicare beneficiaries will be paying for this benefit, even though there is a statutory limit on the percentage of beneficiaries who will actually exceed the deductible threshold and become eligible for the subsidy. From an economic perspective, and in the interest of equity, the benefits derived from DUR interventions should be made available to all beneficiaries whose premiums are financing the program.

- Inclusion of all beneficiaries is clearly the intent of the Congress. A review of the conference report and correspondence between Members of Congress and HCFA, as well as discussions with committee staff, have all indicated that the intent of the legislation was that DUR should encompass all Medicare beneficiaries.

DESIGN OF THE DUR PROGRAM

- The HCFA should develop a Medicare DUR program that incorporates review and education functions at three levels of the drug therapy process: pharmacist/dispensing level, drug bill processor/claims processing level, and post payment level. As soon as is feasible, the program should include the following elements and requirements at each level:

PHARMACIST/DISPENSING LEVEL

1. The electronic claims processing (ECP) data base and system should enable the pharmacist to:

- Record all drug transactions for all beneficiaries (regardless of deductible status).

- Verify the patient's eligibility and deductible status.

- Review a full screen display of the patient's drug regimen.

- Be alerted by computer prompts to potential mismedication errors.

2. The ECP system should be compatible with that used by Medicaid claims processing, so that pharmacists will not be required to operate separate systems.

3. Nationally standardized physician, pharmacist, and patient identification numbers should be used.

4. Pharmacists should be required to conduct a review of the patient's drug regimen for all beneficiaries and assure that in accord with carefully developed criteria all Medicare patients have access to counseling services regarding appropriate administration of the drug, potential side effects and related therapeutic issues. In cases where a potential ADR exists, pharmacists should consult with the physician and patient when necessary before dispensing the drug.

Discussion:

The pharmacist/dispensing level is the most critical point at which mismedication errors can be identified and corrected for individual patients. Although there are important functions to be served at the post payment level, reliance on the post payment review to identify and ameliorate suboptimal prescribing for individual patients would be unrealistic given the resource requirements and time delays associated with case by case analysis. For that reason, it is particularly important that the pharmacist have at his/her disposal all necessary information with which to make a clinical judgement about a prescribed medication. Such information should, at a minimum, include the patient's drug regimen.

There is some concern in HCFA that the cost of transmitting the amount of information associated with drug regimens would be prohibitive and that confidentiality concerns would preclude providing patient profile information to pharmacists. Instead, HCFA anticipates providing pharmacists with a one- or two-line display screen that will transmit information on eligibility and deductible status, and provide prompts to the pharmacist based on preprogrammed edits identifying potential ADRs.

A number of arguments support the proposal to provide full screen displays of patient drug regimens:

- Cost is clearly a relative issue and the estimated cost of transmitting drug regimen information should be evaluated against the program and human costs associated with medication errors. An assertion that the more elaborate system would be prohibitive is not meaningful unless its cost is measured in the context of the cost of not providing drug regimen information to the pharmacist.

- In calculating costs, it should be noted that the information technology industry is in a state of rapid advancement. It is reasonable to expect that the cost of transmitting information today may be significantly greater than the cost would be when the drug benefit becomes effective.

- Although a system of prompts to alert pharmacists to potential ADRs would be a useful tool and should be included in the data system, it cannot substitute for the judgement made by a pharmacist. As mentioned previously, ample research indicates that when pharmacists are provided sufficient information about the patient's drug regimen and engage in review and consultation with physicians and patients, significant improvements can be made in physicians' knowledge base, in patients' compliance behavior, and in overall quality of drug regimens. Further, it is difficult to imagine that even the most elaborate programming could encompass most significant ADR risks. ADRs are not confined to drug interactions, which may be the easiest category to define. The pharmacist who has face-to-face contact with the patient is in a position to engage in an interactive assessment, and to evaluate elements such as dosage levels based on body size, concurrent use of OTC drugs, and the appropriateness of the prescribed drug for the particular condition of the patient. None of these elements can be assessed by a programmed computer that would be relied upon if only prompts are provided to the pharmacist.

- The conference report itself specifies that "participating pharmacists will review the medication profile of beneficiaries for potential adverse reactions before filling prescriptions" (Conference Report, p. 191). Given this statutory requirement, it would appear to be difficult to justify providing pharmacists with a system that does not include regimen information. Further, in interviews with our expert panel as well as discussions with researchers and practitioners in the field, there was widespread agreement that the pharmacist should be provided with patient medication profile information, if any meaningful utilization review is to take place at the dispensing level.

- The issue of confidentiality should receive thorough attention and safeguards can and should be developed to protect the privacy of Medicare beneficiaries. In that respect, it is useful to note that some major pharmacy chains have implemented just such a system with the support of legal opinions that have analyzed the confidentiality aspect. Patient profile records are already maintained as a standard practice in most pharmacies for drugs purchased at that site, and pharmacies are already liable for protection of patient information. In terms of including price and names of other pharmacies used by the patient, those items can be easily coded to protect access to competitors' pricing schedules.

As mentioned previously, preprogrammed edits that will provide prompts to the pharmacist prior to dispensing a drug should also be an integral part of the system. Those edits which would occur when a potential ADR is identified should be detailed subsets of standardized DUR criteria developed at a national level and used as an operating framework by all providers of the electronic claims processing system.

In terms of nationally standardized identification numbers, it is essential that such a system be developed for purposes of tracking mismedication problems and targeting patients and providers for post payment DUR interventions. The Drug Enforcement Administration (DEA) has in place an identification system for most physicians. The HCFA should explore the possibility of adapting this existing DEA system to the needs of it own DUR system.

DRUG BILL PROCESSOR/CLAIMS PROCESSING LEVEL

The drug bill processor should:

1. Utilize prepayment edits to identify cases of duplicate and erroneous billing, and perform other program integrity audit functions on a retrospective basis to identify cases of fraud and abuse.

2. Evaluate the quality of information supplied by the drug bill processor to pharmacists and assess the range and nature of the use of that information by pharmacists.

3. Conduct some automated therapeutic review.

Discussion:

Given the fact that the quantity and quality of counseling provided by community pharmacists is relatively uneven, it will be necessary to establish some monitoring system to assess the performance of participating pharmacists. That function should be conducted at the drug bill processor level with the data available from the ECP data base and with the use of performance audits. Even the most elaborate data system would not ensure that the community pharmacist will actually use the data to conduct reviews and provide counseling services to the physician and/or patient. Consequently, some review mechanism will be required to evaluate performance and ensure quality of care review at the dispensing level.

One example of automated therapeutic review at this level would be cases in which a prescription has not been filled because it duplicates a drug already in the patient's regimen and prescribed by another physician. In such an instance, the drug bill processor could notify all physicians concerned by mail in a timely fashion. Functions such as this one could be carried out using automated review and notification, and would not require a case review.

POST PAYMENT LEVEL

At the post payment level the following functions should be carried out:

1. Using claims data collected at the drug bill processor level, a review of prescribing and utilization behavior should be conducted to identify physicians, pharmacists, and patients who demonstrate patterns of mismedications and to target those groups for education efforts.

2. Once groups are targeted, education strategies should be implemented at the local level and outcomes from such interventions should be monitored and evaluated for effectiveness.

Discussion:

The post payment level of review should be focused exclusively on quality of care and remedial and education efforts. For DUR purposes, post payment review interventions do not appear to be particularly effective in remedying mismedication cases for specific patients. Rather, a review of post payment interventions indicates that their greatest potential is in identifying *potential patterns* of mismedication.

Education efforts are most appropriately placed at this level where they can be tied directly to the targeting process. Further, because a variety of educational interventions will be implemented, particularly in the initial stages of the program, it will be important for each technique to be monitored from a benefit/cost perspective.

IMMEDIATE ACTIONS

The HCFA and PHS, individually and collaboratively, should promote improvements in the prescribing, dispensing and utilization of drugs for older adults by taking the following actions:

- Make funding available for research and demonstration projects that will test DUR interventions and evaluate relative benefit/cost of each.

Discussion:

In order for HCFA to develop an effective DUR program, more elaborate and broader based research will need to be conducted. The limited research that has already been completed and is underway will be useful in providing general direction, but not adequate to equip decision makers with refined policy options. According to congressional staff interviewed in the course of this study, the primary reason behind the decision to begin collecting revenues through the supplemental premium prior to program start-up was to provide funding for demonstration projects. Thus, funding of a demonstration program appears to be consistent with congressional intent.

Requirements for funding of projects should be flexible enough to allow for the testing of innovative DUR strategies with particular attention to educational intervention and should permit a broad range of providers (e.g., PRO's, private researchers, carriers) to compete for funding. However, several basic requirements should shape the overall demonstration effort:

  - All interventions should be measured from a benefit/cost perspective.

  - Some DUR interventions should also be focused on quality issues related to use of OTC as well as prescription drugs. This appears to be one of the areas with the greatest need for additional research. The elderly consume OTC drugs at an even more disproportionate rate than prescription drugs, and, with more potent drugs being reclassified for OTC use, this aspect of drug consumption behavior has serious implications for the broader mismedication problem.

  - Demonstration project findings should be generalizable for the Medicare population and interventions should be measured for effectiveness both in identifying problems *and* affecting clinical changes in behavior. Detection of inappropriate medication practices will not be useful unless it can be linked directly with strategies that produce well documented improvements.
  - A variety of projects should be funded to test interventions with the three primary target populations: physicians, pharmacists and patients. As the findings indicate, the problem of mismedication among the elderly reflects systemic problems at all three population levels.
  - Some projects should also be geared to development of ADR edits that will ultimately be programmed for use in the ECP system.

- Establish a blue-ribbon panel to: (1) develop DUR criteria that will serve as a national guideline for DUR programs carried out throughout the country; (2) make specific recommendations regarding expansion of curricula in U.S. medical schools in the areas of pharmacology and geriatrics; and (3) make additional policy recommendations, as needed, in regard to improving drug utilization among the elderly.

Discussion:

In order to design an effective post payment DUR process it will be necessary to develop general criteria that reflect high risk categories of drug treatment. This should not be confused with the Act's requirement that the Secretary, using compendia published by the American Medical Association and other professional groups, establish standards for use for each covered outpatient drug (see p. 192, Conference Report). Rather, criteria in this context refer to treatment issues (e.g., the use of prescription sleeping pills by the elderly) that are associated with high risk patterns of drug therapy.

The development of standardized criteria is not a particularly novel strategy. In States that do conduct post payment therapeutic DUR (e.g., Minnesota, PACE) establishment of criteria is considered a necessary first step and serves as the basis for more specific and elaborate DUR activities at the local level. The panel should include clinical pharmacologists who specialize in geriatrics, selected medical specialists, and others knowledgeable in drug utilization review. The development of criteria will be an evolutionary process and will require periodic review and revision throughout the life of the drug benefit program. All criteria proposed by the panel should be subject to a public review and comment process.

The issue of medical school curricula development should be the second focus of this group. As outlined in the findings section, it does not appear that the nation's medical schools are adequately prepared to train physicians in the area of geriatric pharmacology during a period when the elderly population is steadily growing. The panel should assess this apparent problem more thoroughly and make recommendations regarding the appropriate Federal role in filling this educational gap.

It is recommended that HCFA collaborate with the National Institute of Aging (NIA) in designing and monitoring the demonstration program and that NIA take an active role in selecting panel members and managing panel activities. The NIA has long been concerned with drug therapy for older adults and with the issue of adequate training for physicians in geriatric pharmacology and can serve as a valuable resource in this process.

- Expedite issuance of FDA guidelines to manufacturers to ensure adequate testing of drugs on elderly populations.

Discussion:

If any commitment to reduce the incidence of mismedication of older adults is to be made by the Department, it must include the finalization of FDA regulations regarding drug testing. Even though some progress has been made in this area, the finalization of these guidelines will serve to reinforce that progress and to signal the Department's commitment to improving the drug testing process as it relates to the elderly.

COMMENTS

Within the Department of Health and Human Services, the Health Care Financing Administration (HCFA) and the Public Health Service (PHS) provided comments. The American Medical Association (AMA), the National Association of Boards of Pharmacy (NABP), the American Association of Colleges of Pharmacy (AACP), the National Association of Chain Drug Stores (NACDS), the Pharmaceutical Manufacturers Association (PMA), and the Public Citizen Health Research Group also commented.

These commenters expressed considerable support for the concept of drug utilization review. The AMA, the AACP, the NABP, the Public Citizen Health Research Group and the PHS indicated much support for our recommendations, but the other commenters, and to a lesser degree the PHS, raised a number of concerns about them.

Chief among these were the costs of DUR and the possible privacy infringements. Also prominent was a concern about how much emphasis ought to be placed on prospective DUR and in particular on the clinical role of pharmacists. Finally, both HCFA and NACDS expressed a strong desire that nothing be done to impede the efficient and timely implementation of the electronic claims processing system. They assert that this undertaking will be complex and difficult enough without introducing elaborate drug utilization review requirements.

We recognize that the establishment of a national DUR program is a complex undertaking that must be carried out carefully, with broadly based input, and over time. We also recognize the enormity of HCFA's responsibility in establishing an ECP system that can handle an estimated 700 million claims in 1991, in developing an on-line transaction mode, and in enrolling participating pharmacies.

At the same time, we must reassert that the well-documented mismedication problems facing the elderly are quite serious and ought to be carefully addressed as part of HCFA's planning for the new drug benefit. At a minimum, nothing should be done initially to preclude the development of a comprehensive drug utilization review system. It is in that context that we offer a wide range of recommendations for consideration of all affected parties. In appendix I, we present, in full, each set of comments and respond to each of them.

APPENDIX I

DETAILED COMMENTS ON THE DRAFT REPORT AND OIG RESPONSE

HEALTH CARE FINANCING ADMINISTRATION COMMENTS

We have reviewed the draft report which presents a comprehensive view of what the OIG believes the ultimate DUR program should entail and accomplish. We agree that HCFA's DUR program must improve quality of care, avoid unnecessary Medicare and personal expenditures, and maintain program integrity. HCFA intends to give appropriate consideration to and review of potential DUR activities at all levels of the drug delivery system throughout our design process. Our specific comments are attached.

As we develop a DUR system, we must make it flexible enough to allow for necessary modifications to attain additional programmatic goals as time and resources permit.

Thank you for giving us the opportunity to comment on this draft report.

Development and Design of DUR Program

We are concerned that the report does not adequately address the fact that in order to develop a realistically designed DUR system, it must be considered within the context of the current estimates for the Catastrophic Drug Program (i.e., benefit outlays, revenues, administrative costs, and claims volume). The HCFA's DUR system, which will be complex and unlike any other existing system, must be able to accommodate an estimated 700 million claims in 1991. The OIG does not appear to recognize this when discussing either pharmacy or fiscal intermediary (FI)/carrier criteria. For example, the OIG emphasizes certain one-on-one counseling and education activities for physicians, pharmacists, and beneficiaries, again without any acknowledgment of the possible number of encounters for these populations (e.g., 34 million beneficiaries).

The OIG's recommendations must be evaluated within the self-financing design of the Catastrophic Drug Program. Congress set rigid program income and outlay factors through 1993 that severely limit HCFA's flexibility. Benefit costs in the drug program are uncertain, but HCFA has consistently maintained that the financing will be inadequate. Although OIG claims that benefit savings will accrue if its suggestions are implemented, we must first spend the requisite dollars for those activities before the savings will occur. Also, the money to finance those activities must be available, especially research and demonstration dollars. The President's Fiscal Year (FY) 1990 budget now projects FY 1991 funding for DUR payment safeguard activities to be approximately $16.1 million ($4.3 for Medical/Utilization Review and $11.8 for Pharmacy Audits).

Within this framework, implementation of any of the OIG's recommendations would add significant additional administrative costs. For example, HCFA has planned for the drug processors (DPs) to provide the pharmacists with two lines of information: i.e., whether the beneficiary is eligible and the amount of co-payment, if any. (There will be an additional response if there is the potential for any adverse drug reactions.) The OIG suggests that the DPs provide the pharmacists with a full screen of information concerning the beneficiary's drug regimen. Although this recommendation has considerable merit, HCFA anticipates the cost of transmitting the planned two lines of information to the pharmacists to be $441 million for FY 1991. The cost of providing an additional screen of information as recommended by the OIG would probably be proportional and would be prohibitive without additional revenue from beneficiaries. There are also beneficiary privacy and confidentiality concerns that would have to be addressed.

Although we concur with the general approach recommended for the DUR program, it must take into account, in addition to cost limitations (1) patient privacy and confidentiality, (2) time considerations inherent in an on-line transaction processing mode, (3) equipment and software cost implications and (4) pharmacy enrollment concerns. All these elements will have to be carefully weighed in designing the entire system.

Through the Part B Data Policy Workgroup, we have been identifying those data elements which HCFA would require to support studies that review prescribing and utilization behavior of physicians, pharmacies, and beneficiaries. These drug data are to be linked to other claims data to develop patients' histories for use in designing and testing prospective utilization review screens. We will continue to consider the data needs of the DUR as implementation models are determined.

The OIG recommends that the system should enable the pharmacist to be alerted by computer prompts to potential mismedication errors. While we do not disagree, drug-related problems are not confined to drug interactions. The pharmacist who has face-to-face contact with the patient is in a unique position to engage in an interactive assessment of the patient and to evaluate elements such as dosage levels based on body size, concurrent visits to other health care practitioners, concurrent or recent use of prescription or non-prescription drugs or other treatment remedies, the appropriateness of the prescribed drug(s) for the particular condition of the patient, and other factors that influence the patient's welfare. None of these elements can be assessed by a computer-based system. In evaluating a patient's drug regimen and making a judgment as to the level of counseling, the pharmacist assesses the significance of the problem. Is the problem significant enough to contact the physician and/or is the problem of such a degree that it is obvious to the patient (requires no intervention on the part of the pharmacist)?' This is a professional judgment. In some cases, a professional judgment is made, based on the pharmacist's knowledge that it is better not to discuss a certain issue or problem with a patient. Therefore, since the degree of patient drug counseling is a professional judgment decision, we believe it should be left to the pharmacist, and that the system is merely a tool to facilitate application of that professional expertise.

It probably is not feasible to make our system compatible with those used for Medicaid claims processing. All of the State systems have been developed independently, and there is considerable variation among them. Therefore, no system established by Medicare could fit perfectly with all State systems unless the States moved toward standardization. We are attempting to mesh our system with Medicaid as much as feasible, including obtaining input from the State Pharmacy Technical Advisory Group. However, it is not possible to make the Medicare and Medicaid systems fully compatible.

The OIG is recommending that pharmacists should be required to provide counseling to all beneficiaries regarding appropriate administration of a drug, potential side effects, and related therapeutic issues. The Medicare Catastrophic Coverage Act (MCCA) requires participating pharmacies only "to offer" to counsel each Medicare beneficiary. While we agree with the emphasis expressed by the OIG concerning the importance of counseling, the language of the Act does not necessarily mean that each patient must receive counseling, especially if counseling is intended to mean verbal counseling. Moreover, not every patient may want or require counseling.

On page 31 of the report, it is recommended that the results of drug utilization review be used to educate physicians, pharmacists, and patients. The report recommends that education strategies are to be implemented at the local level and outcomes from such interventions should be monitored and evaluated for effectiveness. We note that, while section 202(b)(5)(A) of MCCA requires education programs for physicians and pharmacists, patients are not specifically mentioned. Consistent with the law, we believe Federal education programs should focus on physicians and pharmacists. In turn, as physicians and pharmacists become more informed about drugs, they would be prepared to provide better drug education to their patients.

Make Funding Available for Research and Demonstration Projects

HCFA already has a number of initiatives under way as a result of the enactment of the MCCA. In order to assess the impact of the new benefit program on cost, access and utilization, studies have been required, as well as a series of demonstration projects.

Currently, we have a research and demonstration process under way to receive and award possible projects related to the new drug program. These awards may include studies relating to effectiveness, appropriateness, and cost patterns of drug usage in the Medicare population.

Establish a Blue-Ribbon Panel to Develop DUR Criteria

Establishment of a blue-ribbon panel to develop DUR criteria to serve as a national standard for DUR programs is a noteworthy idea as it applies to Medicare. However, we believe development of Medicare DUR criteria for use as a national standard by the private sector is beyond HCFA's purview. Additionally, use of Medicare DUR standards for possible inclusion in medical school curricula and to improve drug utilization among the elderly are ideas that would better be handled by groups outside HCFA designed for that purpose.

State Medicaid DUR Efforts

While it is true that many States focus the majority of their efforts on program integrity to reduce fraud, waste, and abuse, nearly all States have programs to enhance the quality of care provided their beneficiaries with regard to pharmaceuticals. While the draft report highlights Minnesota's noteworthy program in this regard, it fails to cite other States which have developed very effective DUR programs.

Two of the best examples can be found in Medicaid programs which have high percentages of elderly beneficiaries: Florida and California.

Florida--Quite apart from the activities of Florida's Program Integrity Office, the Medicaid Pharmacy Consultant in this State serves as project leader on a DUR program which focuses on the therapeutic value of its drug program. Drug-to-drug interactions, poly-pharmacy dispensing practices, and patients with cardiac, respiratory, digestive, and diabetic disorders are key decision parameters used in building Florida's patient profiles. Utilizing committees of pharmacists and physicians, Florida sends letters to prescribing providers when a potential problem is identified, with follow-up letters or phone calls in 30 days. Jerry Wells, R.Ph. Pharmacist Consultant (904-487-4441), may be contacted for additional information.

California--Currently, this State is analyzing the effect of its DUR programs on two large population groups which have been statistically selected based upon urban/rural, age, contraindications, and disease types to learn of the therapeutic as well as financial benefits of their Program. Similar to Florida's system in that individuals are identified based upon decision criteria Previously selected, follow-up is 30 and 60 days apart. Carlo Menotti, R.Ph. (916-324-2477) is the person in charge of this program.

Technical Note

The Medicare drug program is a Part B benefit and will be generally administered by special contractors (drug bill processors), rather than the fiscal intermediaries to which the report refers.

OIG RESPONSE TO HCFA COMMENTS

While HCFA does not disagree with the overall directions we set forth for the development of a Medicare DUR program, it indicates that considerations involving cost, complexity, and privacy preclude any major progress in carrying out these directions in the near term.

We agree that there are important considerations concerning cost, complexity, and privacy that must be addressed. However, given the scope of the problems involving adverse drug reaction among the elderly, we do feel a sense of urgency in addressing the above-noted considerations. The phasing in of a multi-faceted DUR program can have a very positive effect on the well-being of thousands of Medicare beneficiaries. Moreover, it is worth noting that since in a given year less than 20 percent of the beneficiaries will reach the deductible threshold and thus become eligible for partial coverage of the costs of their prescription drugs, the DUR program looms as the major drug-related benefit that most beneficiaries will receive for their increased financial contribution.

Our recommendations to HCFA, we must underscore, call for immediate action in planning a comprehensive Medicare DUR program and for its implementation "as soon as is feasible." We recognize that the program must be phased in and that refinements must regularly be made based on operational experience and on research and demonstration results. In this regard, it is particularly important that at the outset HCFA express its commitment to develop a comprehensive, well-designed, and cost-effective DUR program and assure that its initial actions in establishing the electronic claims processing system are consistent with that commitment.

On the matter of privacy, in accord with discussions with HCFA officials, we conducted some follow-up inquiry and issued a management advisory report entitled "Privacy Implications of the Medicare Prescription Drug Benefit's Electronic Claims Processing System" (OAI-01-89-89170). This brief report, based largely on meetings with privacy advocates, indicates quite clearly that with proper safeguards, privacy considerations would not preclude the development of the comprehensive DUR system outlined in our report.

With respect to the remaining HCFA comments on the report, we respond briefly to each of them below.

On the Role of the Pharmacist. The HCFA points out that "drug related problems are not confined to drug interactions" and that the pharmacist "who has face-to-face contact with the patient is in a unique position to engage in an interactive assessment of the patient" and to make evaluations on matters such as dosage levels. It later adds that "since the degree of patient drug counseling is a professional judgment decision, we believe it should be left to the pharmacist, and that the system is merely a tool to facilitate application of that professional expertise."

It is because we believe that it is important to reinforce the pharmacists' role in providing professional counseling that we are urging HCFA to provide the pharmacists with full screen displays of patient drug regimens as soon as is practical. Without such information, we feel the application of the pharmacists's "professional expertise" would be seriously hampered, particularly with respect to the many patients who visit multiple physicians and/or pharmacies.

On the Compatibility of Medicare and Medicaid Claims Processing Systems. We recognize the difficulties involved in achieving full compatibility of these systems. We are pleased that HCFA is attempting to mesh the systems "as much as feasible." We urge that full compatibility be embraced as a long-term goal.

On the Language of the Medicare Catastrophic Coverage Act Concerning Pharmacist Counseling. In interpreting the statutory language and in its forthcoming regulations, we urge that HCFA not engage in an overly narrow interpretation of "counseling." We feel it is important for the pharmacists' responsibility "to offer" counseling to be clearly stated and defined. A study we are conducting concerning the clinical role of the community pharmacist will offer some suggestions in that regard.

On the Importance of Patient Education. We agree that the Medicare DUR program should concentrate on physician and pharmacist education. However, we believe that there is also an important role for patient education which HCFA ought not overlook. Some innovative systems are now being developed to facilitate direct patient access to drug information. The HCFA, in consultation with the Public Health Service and Medicare beneficiary advocacy groups, should review them to assess their effectiveness and to determine how they might be incorporated into a comprehensive DUR effort.

On the Establishment of a Blue-Ribbon Panel. The HCFA comments that it does not feel it would be appropriate for it to participate on a blue-ribbon panel that would develop DUR criteria to serve as a national guideline for DUR programs and to make specific recommendations regarding medical school curricula in the area of pharmacology and geriatrics. As we indicated in the report, we feel it is extremely important to have Departmental leadership in these areas. The American Medical Association, as noted in its comments on our report, expresses its support for such a panel (provided that the representation of members is sufficiently diverse and that proposed criteria are subject to a public review and comment process). The PHS also expresses its support for the panel.

On State Medicaid DUR Efforts. We underscore that most State Medicaid DUR efforts are aimed at identifying and correcting problems of program integrity, rather than quality of care. This reality became quite clear from our State survey. At the same time, we recognize that States other than Minnesota have initiated therapeutically oriented DUR efforts. In elaborating on the Minnesota program, we sought to explain the approach of one State that has long been involved in this area. We welcome HCFA's explanations of the efforts underway in Florida and California.

On the Term "Fiscal Intermediaries". In our draft report, we used the term "fiscal intermediaries" in a generic sense, not in reference to Medicare Part A Fiscal Intermediaries. We recognize that the Medicare drug program is a Part B benefit and will be generally administered by special contractors or drug bill processors. To avoid any confusion, we have used the term "drug bill processors" rather than "fiscal intermediaries" is the final report.

PUBLIC HEALTH SERVICE COMMENTS

General Comments

We express general concern that the evidence presented in the OIG draft report to support the findings of mismedication among older adults may not have been based on objective information. The OIG report relies on secondary sources such as anecdotal evidence and unpublished reports as the basis for the findings. We believe that findings of this significance should be supported by incontrovertible data, preferably data that have been peer reviewed and published in medical and scientific documents. A more detailed explanation of our concern is provided in the technical comments.

Since 1981, the Food and Drug Administration (FDA) has worked closely with the National Council on Patient Information and Education (NCPIE) to coordinate the development and implementation of major patient education initiatives in the public and private sectors. In 1987, NCPIE released the report, "Priorities and Approaches for Improving Prescription Medicine Use of Older Americans." The OIG draft report does not reference the NCPIE report or its programs. We recommend that the NCPIE report and programs be incorporated in the OIG report. In addition, FDA issued a report, "Prescription Drug, Medical Device, and X-Ray Patient Education Activities," that highlights FDA's current activities in this area. We also recommend that such activities be cited in the report.

The following are comments on the OIG recommendations.

OIG Recommendation

The HCFA should develop a Medicare DUR program that incorporates review and education functions at three levels of the drug therapy process: pharmacist/dispensing level, fiscal intermediary/claims processing level, and post payment level.

PHS Comment

Even though this recommendation is directed to HCFA and we generally concur with the recommendation it appears that two highly significant issues must receive further consideration. These are (1) the confidentiality of a patient's drug regimen and (2) questions about the adequacy of the quality of the HCFA database for reliable therapeutic review.

(1) Confidentiality

The prescription of certain drugs is strongly associated with certain diagnoses, e.g., neuroleptics with psychotic disorders and AZT with AIDS.

What measures will be taken to ensure the confidentiality of a patient's drug regimen?

Will clerks and other non-professional pharmacy personnel have access to the computerized database?

Will a patient have the right to request that his drug regimen not be included in the drug database?

We believe that these issues require further attention prior to the implementation of a national program.

(2) Quality of the HCFA Database

Although the report recognizes the limitations of the HCFA database for the purpose of therapeutic review, the recommendation states that the fiscal intermediary should "conduct some automated therapeutic review."

The results of automated therapeutic review utilizing the HCFA database will not be reliable because of the inadequacy of the diagnostic information included in Medicare Part B claim forms. Geriatric patients commonly suffer from multiple diseases requiring complex drug regimens. A drug used to treat one disease may have side effects which have an adverse impact on a second disease. Therefore, a complete list of accurate diagnoses is important for therapeutic review. Researchers experienced in the use of automated Medicaid databases are concerned that the quality and lack of comprehensiveness of the diagnostic information which will be available in the HCFA database will result in erroneous conclusions if this information is used for therapeutic review. A conference which will include discussion of this issue is currently being planned by the Institute of Medicine (IOM).

Following the IOM conference, HCFA should consider funding research directed towards modeling various methods of therapeutic review using existing databases to reveal the potential and limitations of different approaches to this problem. This might help avoid future large scale problems which will result if the HCFA database is asked to serve purposes for which it is not adequately designed.

OIG Recommendation

The HCFA and PHS, individually and collaboratively, should promote improvements in the prescribing, dispensing and utilization of drugs for older adults by taking the following actions:

- Establish a blue ribbon panel to (1) develop drug utilization review (DUR) criteria that will serve as a national guideline for DUR programs carried out throughout the country; (2) make specific recommendations regarding expansion of curricula in U.S. medical schools in the areas of pharmacology and geriatrics; and (3) make additional policy recommendations, as needed, in regard to improving drug utilization among the elderly.

PHS Comment

We concur. The National Institute on Aging, NIH, will collaborate with HCFA in designing and monitoring the demonstration program and will also participate in selecting panel members and managing panel activities.

OIG Recommendation

- Expedite issuance of FDA guidelines to manufacturers to ensure adequate testing of drugs on elderly populations.

PHS Comment

We concur. Guidelines have been circulated in draft form which we believe drug sponsors have been following. One element of the proposed guidelines that sponsors analyze beneficial and adverse effects to see whether there are age related differences in response was incorporated into the "Guideline for Clinical and Statistical Sections of an Application," which was published in final in mid-1988. Other aspects of the guideline such as studies to determine better the effects of abnormal kidney or liver function on the excretion of the drug are also being implemented by drug companies.

We disagree, however, with the assertion that mismedication among older adults is a consequence of inadequate drug testing among elderly populations. The report states that studies required to secure FDA approval are typically performed on relatively healthy young adults for products that will be prescribed to elderly patients. Although Phase I clinical trials in small numbers of subjects are normally performed on healthy volunteers, these early trials are a tiny fraction of the overall drug exposure and are concerned primarily with initial safety of the drug. Elderly patients have regularly been included in Phase II and III studies, which are the largest studies concerned with efficacy, side-effects and risks in persons with disease to be treated by the drug. In 1983, FDA conducted a brief study on age distributions of patients in clinical trials of 12 marketing applications. It covered a good representation of patients in their sixties and seventies, and whether the disease being treated was common in those age groups.

FDA provides information to physicians and other health professionals concerning the use of drug products. This is accomplished primarily through the products' labeling that must be approved as part of the new drug application process. In another recent study, FDA reviewed the labeling of new molecular entities approved during 1987 and 1988 and found, after excluding some special cases such as topical and cancer drugs, that about 50 percent carried some information relating specifically to the elderly. Further, not all products require special instructions for geriatric use.

FDA is currently developing a regulation to be incorporated into 21 CFR 201.57, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs," which will require a geriatric use section in the labeling of human prescription drugs.

Technical Comments

- Page 3, FINDINGS, Second Paragraph

The sentence "Anecdotal evidence from State pharmaceutical assistance programs for the elderly . . ." implies that existing mismedication problems may be exacerbated by new benefits. We believe that stronger evidence should be used to support this finding.

-Page 4, Second Full Paragraph

The report states that "Although Americans who are 65 years or over currently constitute only 12 percent of the population, they use over 30 percent of the prescription drugs and 40 percent of the nonprescription drugs dispensed." This reference is from an unpublished report. We believe that such a statement should be based on inconvertible data and published in a credible peer-reviewed data. Likewise, the next reference cited is from a report which is not peer-reviewed data.

-Page 6, Third Full Paragraph, Second Sentence

The report states that "32,000 hip fractures are incurred annually due to drug-induced falls." The report does not provide substantiating data.

Further, the report states that 61,000 older adults developed Parkinson-like symptoms due to the use of antipsychotic drugs. It should be noted that this is a well recognized side effect of certain of these drugs and occurs across all age groups. We believe that the data provided do not allow a conclusion to be drawn that this represents a mismedication problem.

-Page 9, Second Paragraph, Second Sentence, Subsections

The report states that "...the filtering ability of the kidneys decreases by 30 percent by the time a person reaches 65 years...." We believe that this reference is stated incorrectly. It should indicate that the number of nephrons decreases 30 to 40 percent between the ages of 25 and 85 years (Goldman, R. in Wyngaarden and Smith (eds.), *Cecil Textbook of Medicine*, Saunders & Co., 1985).

Also, we suggest that the following be inserted at the end of this statement.

"It should be noted that the above described age-associated changes in body size and composition, liver functions, and kidney functions are subject to wide variation with some individuals showing significantly less change than might be expected for the population as a whole."

-Page 11, Last Paragraph, First Sentence

Two of the OIG references cited for this statement indicate an educational gap in the knowledge of prescribing psychotropic drugs and not a generalized educational gap. We believe the report should be changed to reflect that the educational gap refers to that of prescribing psychotropic drugs.

Endnotes

We note that 32 of the 95 references cited are not peer-reviewed and published in medical or scientific documents. These references include testimony of individuals and interest groups (12 citations) before Congressional committees, OIG "discussions" with "expert panels" (4 citations) and other references including speeches, unpublished articles, newspaper and magazine articles, lectures and presentations, and documents prepared by interest groups such as the American Association of Retired Persons and the Public Citizen Health Research Group. While information reported from these sources may, in fact, be entirely correct, the reader must assume that all of these represent opinions of individuals or groups with variable expertise and interests in the area of concern.

OIG RESPONSE TO PHS COMMENTS

We are pleased with the PHS' generally positive response to our recommendations and with its clarifications, which add to the value of the report. On the matters of confidentiality and the importance of further research and development (particularly in regard to automated therapeutic review and the use of diagnostic codes) we agree that these are vital, sensitive matters warranting serious attention. Our response to the HCFA comments offers some elaboration on both of these matters.

The PHS took exception to the finding that clinical studies are typically performed on healthy young adults. It noted that elderly patients have regularly been included in phase II and III studies, and that guidelines issued in 1988 require that analysis be conducted concerning adverse effects and age-related differences. We made a number of changes in the text to incorporate recent information developed by FDA and to reflect the importance of its recently issued guidelines. We continue to urge the issuance in final of the FDA guidelines to manufactureres to ensure adequate testing of drugs on elderly populations. The FDA agrees with us on this point.

In regard to the more technical comments offered by PHS, we have incorporated into the report and the footnotes a reference to the National Council on Patient Information and Education (NCPIE), a clarification concerning physicians' education gap in the knowledge of prescribing drugs, and PHS' suggested qualification concerning changes in body size and composition and liver and kidney funcitons. With respect to PHS' call for further, peer-reviewed citations, we recognize that there is much additional research that can be conducted on problems concerning the mismedication of the elderly. We urge that scholars undertake such research, both to expand the existing knowledge base and to synthesize the knowledge that already exists. On the basis of our own broadly based review, drawing on insights from peer-review journals and many other sources, the evidence is compelling that there exists a serious problem concerning the mismedication of the elderly.

NATIONAL ASSOCIATION OF CHAIN DRUG STORES COMMENTS

The National Association of Chain Drug Stores, Inc. (NACDS), appreciates the opportunity to comment on the draft report entitled "Medicare Drug Utilization Review." NACDS represents 173 chains drug corporations operating in excess of 21,000 retail pharmacies nationwide that dispense over 40 percent of the nation's prescription drug products. As an integral component of the health care delivery system, NACDS members take seriously their role as the final step in the dispensing process of prescription drugs. As committed health care professionals, NACDS members' paramount concern is the health and well-being of their customers, including the elderly. Historically, retail pharmacy has served as the link between the physician and the patient on proper usage of prescription drugs. This dedication to service and health care is evident by public opinion polls that hold pharmacists as America's most respected health professional.

However, NACDS must register its disagreement with many of the report's assumptions and conclusions. An issue as important as "drug utilization review" (DUR) cannot be decided on the basis of one report and a brief comment period. Examination of this subject in a vacuum ignores fundamental questions and implications for the health care delivery system. The discussion of issues, such as privacy, liability alternatives, and cost, are too important to be avoided. From retail pharmacy's viewpoint, a computer and "star wars" application does not make an effective and quality DUR system. NACDS respectfully submits that subjective science cannot be made objective by imposing mechanical standards.

NACDS also suggests that the report assumes a Congressional intent regarding the imposition of a "mandatory" DUR system that is absent from the actual legislation, the legislative history, and accompanying conference history. NACDS proposes that the system envisioned by Congress and that which is suggested by the report are not compatible.

Furthermore, NACDS believes that the report findings are incomplete and based on anecdotal and often, insubstantial evidence, hearsay, and false assumptions. In particular, as to the report "findings" [on] community pharmacy, NACDS disagrees with conclusions that only a "small percentage of elderly patients receive drug counseling services," that "pharmacists do not perform adequate reviews of patients drug regimens"; or "consult with physicians and patients." Counseling and DUR can and should take many forms. Both verbal and non-verbal communication, such as the use of auxiliary labels, have become a routine part of the practice of pharmacy. In essence, the standard of care for pharmacy is such that examination of the patient's drug regimen is conducted on a regular basis.

As to the report's recommendations, NACDS strongly supports the implementation of an electronic claims processing (ECP) system to verify a patient's eligibility and deductible status. These functions alone represent an enormous undertaking--a fact recognized by the

Congress--and surely, one of the reasons Congress did not specify how DUR's and patient counseling were to be conducted. The ECP system is the heart and soul of the program.

Lastly, although NACDS disagrees with the apparent conclusion that mismedication is a national epidemic, we agree that mismedication among any segment of the population must be of concern to all health care professionals. As outlined on page five, paragraph three of the report, mismedication can occur in at least four ways. However, it must be recognized that of the four ways stated, only point number four can be directed specifically to the pharmacist. We find the lack of this fundamental understanding to be most disturbing. NACDS does not believe that the absence of physician accountability to their patient should be attributed to or be the entire responsibility of the pharmacist.

The above presumption indicates an unrealistic assumption and a basic lack of understanding of the role of the pharmacist in a dispensing of prescription drugs. In any system envisioned, the pharmacist will always be operating from an incomplete data base. For example, over-the-counter (OTC) medication is most frequently purchased in non-pharmacy settings. In addition, the growing incidence of physician dispensing of prescription drugs further complicates the report's recommendations.

In conclusion, NACDS hopes that you will continue to review this issue in light of our comments. NACDS hopes that you will contact us to further discuss this important issue.

OIG RESPONSE TO NACDS COMMENTS

We believe NACDS has taken too limited a view of the role of a DUR program and of pharmacists in addressing the problems of mismedication of the elderly.

We responded to a number of the NACDS concerns in our previous comments. In addition, we note that the Catastrophic legislation clearly calls for the establishment of a Medicare DUR program and the conference report specifies that "participating pharmacies will review the medication profile of beneficiaries for potential adverse reactions before filling prescriptions." With respect to the role of the pharmacist, we have been informed by many pharmacists and by much literature that the counseling and consultation practices may indeed involve more than identifying inappropriate combinations of drugs. Our understanding is that the professional training of pharmacists increasingly prepares them for a broader role that enables them to identify various kinds of mismedication problems.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION COMMENTS

Your report, "Medicare Drug Utilization Review," focuses attention on the need to ensure that older people receive and use appropriate medicines and on the potential benefits of a Medicare drug utilization review system.

The Pharmaceutical Manufacturers Association recently completed a series of surveys that show its enormous commitment to discovering and developing medicines that will help older people live longer, more productive lives. The results showed that the research-based pharmaceutical industry is developing 221 medicines to treat 23 diseases prevalent among older people. The pharmaceutical industry will invest an estimated $3.6 billion in research on diseases of the aging in 1989--approximately half of its projected $7.3 billion research and development budget for this year.

Because of the industry's role in discovering and developing medicines for older people, we are very concerned that information about the research and development process be accurately portrayed. PMA is particularly concerned about the Report's assertion that clinical studies on new drugs for use in older people are typically performed on healthy young adults for a short period of time. This, however, is only the *first* phase of human testing--a multiphase process that averages 6 years to complete. In subsequent phases, new drugs for the elderly are tested for years on large numbers of older people, because they are the people with the conditions that the drugs are intended to treat.

FDA reports that today's New Drug Applications contain data on an appropriate number of older people, indicating that the pharmaceutical industry is observing testing guidelines even though these guidelines have not been formally adopted by the FDA.

In addition, we wish to note that PMA supports the following principles:

- Older people should obtain a primary-care doctor to coordinate their care, because older people are more likely to have several conditions that require that they see a variety of specialists and take a complex regimen of prescription drugs. This helps explain why older people use a higher proportion of pharmaceuticals and experience more medicine-related side effects.

- Older people should take their medication according to their doctors' instructions. Noncompliance with medication instructions results in problems of undermedication as well as overmedication.

- Medical education authorities should emphasize programs that ensure physicians become aware of key principles in the emerging field of geriatric medicine.

Regarding drug utilization review, PMA supports the DUR provisions of the 1988 Medicare Act and appropriate DUR programs at the state Medicaid level. Accordingly, there are several points about DURs that we wish to emphasize in response to your report:

- PMA believes that the critical objective associated with drug utilization review is to improve the quality of care. Whether this will reduce drug program costs is not a certainty, because DUR would likely identify cases where there is a serious "under-utilization" of prescription drugs (which could actually increase drug program costs). Therefore, it is more appropriate to focus on the fact that DUR may improve quality and yield savings for *overall* health care costs.

- PMA believes that the objective of maintaining program integrity should be a key component of Medicare DUR. The Report asserts that Medicaid DUR policies have "limited applicability" for Medicare because of their emphasis on fraudulent or abusive activities. PMA believes the value of this area of DUR should not be underestimated. Instances of fraud and abuse may be quite costly, are easily identifiable and may have a major impact on the integrity of the Medicare program.

- PMA believes that the Report may be overly optimistic about the capabilities of prospective DUR. Experts in the DUR field have raised serious questions about the ability of the point-of-sale system envisioned by HCFA to accomplish prospective DUR. Besides questions about its feasibility, prospective DUR raises additional concerns about safeguarding patient confidentiality and to avoiding unnecessary interference in the patient/physician and patient/pharmacist relationships.

- PMA believes that, given the lack of experience of applying DUR to an outpatient drug program with over 700 million claims, it is essential that deliberations and ultimate decisions on Medicare DUR be open to input and debate by the public and scientific community.

We hope that these comments are helpful in continuing a productive exchange of ideas on the beneficial use of medicines by older people and in implementation of the DUR component in the new Medicare outpatient prescription drug benefit. Please let me know if you have any questions or if we can be of any further assistance.

OIG RESPONSE TO PMA COMMMENTS

Maintaining program integrity certainly should be an objective of a Medicare DUR program. However, given the documented scope and severity of adverse drug reactions among the elderly, we feel there is a solid basis for devoting primary attention to this issue.

How much attention ought to be placed on prospective DUR at the start is a question warranting further inquiry. We feel counseling and consultation efforts at the point-of-sale can have a valuable preventive effect. However, we recognize that there is much to be learned in this area and that research and demonstration efforts can be useful in that regard.

We continue to feel that the issuance of FDA guidelines to manufacturers would help to prevent mismedication resulting from lack of attention to the special conditions of elderly patients.

AMERICAN MEDICAL ASSOCIATION COMMENTS

The American Medical Association (AMA) is writing to express its views concerning the draft report of the Office of the Inspector General (IG) entitled, "Medicare Drug Utilization

Review." The stated purpose of the report was to "foster the development and implementation of an effective Drug Utilization Review (DUR) system under the Medicare program. Toward this end, it sought to promote a better understanding of the major problems and needs that a DUR program should address, and of the relevant insights that emerge from research and experience."

The AMA believes that, in general, this report presents an appraisal of potential contributors, i.e., the Food and Drug Administration, manufacturers, physicians, pharmacists and elderly patients, to any problem of mismedication in the elderly. The AMA agrees with the report's recommendation for an effective DUR system that places major emphasis on improving the quality of patient care with education as the primary remedial strategy. The AMA is particularly pleased that the IG's report recognizes that improving the quality of care is vitally important and should result in significant savings in the overall cost of the Medicare program. The Association also agrees that the DUR program should be applicable to all beneficiaries regardless of deductible status.

The IG's recommendation for the establishment of a "blue-ribbon panel to develop DUR criteria" is consistent with the AMA's proposal to the Health Care Financing Administration (HCFA) for a government-funded Drug Utilization Review Board to manage the DUR program. The AMA agrees with the IG that representation of gerontologic specialists is essential for optimum function of a DUR Board. We recommend, however, that the Board also should include representation of clinical pharmacologists who specialize in geriatrics. In addition, representation of individuals from other disciplines (e.g., selected medical specialists, physician experts in medical quality assurance, pharmacists and physicians knowledgeable in drug utilization review, pharmacoepidemiologists, and biomedical statisticians) will enhance the DUR Board's effectiveness. The AMA recommends that all proposed criteria emanating from the DUR Board be subject to a public review and comment process.

One of the proposed functions of the IG's proposed blue-ribbon panel would be to "develop general criteria that reflect high-risk categories of drug treatment", presumably to serve as prospective standards for post-payment DUR studies. We have two recommendations concerning this issue. First, any such prospective standards developed should be based on adequate documentation in the peer-reviewed medical literature, reflect a strong consensus of practicing physicians, and be subject to public review and comment.

Second, the AMA takes exception to the IG's statement on page 33 of the report that AMA's *Drug Evaluations*, one of the compendia named in the Conference Report to P.L. 100-360, is not a resource for the development of general criteria that reflect high-risk categories of drug treatment. *Drug Evaluations* is a comprehensive, consensus-derived compendium designed to offer physicians unbiased and clinically relevant discussions of drug selection guidelines for various diseases, disorders or conditions as well as establish standards for outpatient drugs to be covered in the Medicare Catastrophic Coverage Act. Evaluations of drugs in *Drug Evaluations* may be favorable or unfavorable. This compendium covers both labeled and unlabeled indications and references the medical literature. Thus, it is precisely those general criteria that *Drug Evaluations* does include and that clearly separates it from the two other compendia named in the Conference Report to P.L. 100-360.

The IG report emphasizes DUR at the pharmacist/dispensing level, because it is "the most critical point at which mismedication errors can be identified and corrected for individual patients." The AMA believes that caution should be exercised in implementing *prospective* DUR. While prospective reviews can be effective in preventing adverse drug reactions and in ensuring proper utilization of drugs, the lack of sufficient, accurate and timely patient-related data available to the pharmacist during the point-of-sale process can severely limit the usefulness of prospective DUR. The AMA has strongly recommended against HCFA requiring prospective DUR until the DUR Board (blue-ribbon panel) establishes that such review is valuable and determines what specific types of reviews can be performed effectively. Funding for demonstration projects in this very important area should be provided.

The AMA also is concerned that the amount of time devoted specifically to gerontology and clinical pharmacology education may be inadequate and needs to be addressed. A need exists for innovative strategies of continuing education to extend the training of physicians in these disciplines into the postgraduate and active-practice years.

The AMA appreciates the opportunity to express its views. We urge you to consider carefully our recommendations for improving the report.

OIG RESPONSE TO AMA COMMENTS

We are pleased with AMA's generally positive reaction to the report. Below we respond to the three suggestions/exceptions which it set forth.

First, with respect to the blue-ribbon panel, we agree with AMA's comments concerning participation on the panel and public review of DUR criteria developed by the panel. We have made the corresponding changes in the report.

Second, concerning the relevance of the AMA's *Drug Evaluations* as a resource for the development of DUR criteria, we agree that it can serve as such a resource. Our intent in the report is only to distinguish our recommendation calling for the establishment of general DUR criteria from the Catastrophic legislation's requirement that the HHS Secretary establish standards for the use of each covered outpatient drug.

Third, in reference to the AMA's caution concerning prospective DUR, we agree that HCFA must move carefully and that funding for demonstration projects in this area is very important. We recognize, as the AMA points out, that "the lack of sufficient accurate and timely" patient-related data available to the pharmacist during the point-of-sale process can severely limit the usefulness of prospective DUR. It is for that reason that we urge the provision of a full screen drug regimen as soon as practical.

AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY COMMENTS

Thank you for the opportunity to comment on the draft report, "Medicare Drug Utilization Review." On behalf of the nation's 74 colleges of pharmacy, 3,500 full-time faculty and 25,000 professional and graduate students, I am pleased to do so.

The Office of the Inspector General is to be commended for a fine piece of work. It generally and fairly describes the relationship between providers, third-party administrators, payor and post-payment responsibilities. My comments, therefore, will be very specific and focus primarily on pharmacists and their relationship to the system described in the Report.

- Page 15; final paragraph - excellent observation.

- Page 18; first bullet - suggest a Pharmacy and Therapeutics Committee-like structure, thus enhancing physician/pharmacist interface.

- Page 21; discussion about peer review - should separate out and not confuse the process of peer review/DUR from how peer review is applied/enforced. The process may be quite satisfactory while the way we enforce or apply peer review standards on practitioners may be the shortcoming. Further, paragraph 2 on page 21 and Avorn's study, as described on page 22, are consistent with and precisely why peer review works. Page 23, targeting prescribers, is a method of applying peer review.

- Page 24 and others - use of the word "industry." Does this refer to pharmacy practice or the pharmaceutical industry? If the former, I certainly support the use of that terminology.

- Page 26; regarding targeting DUR only for patients exceeding deductible - data collection and DUR should apply to all patients, but various levels of counseling can be identified based on specific patient need (the pharmacy literature supports this observation).

- Page 27; regarding computer prompts to potential medication errors - should be passive only; pharmacists must still realize their responsibilities for ensuring safe and effective drug use.

- Page 28; item 3 - the profession is undergoing a major pharmacy manpower (census) effort, headed by AACP. In order to create the census and maintain it, the profession requires unique identifiers for pharmacists. If the Department and the profession could work together on this aspect of data collection, it would probably benefit both of us.

- Page 28; item 4 - improving prescribing through cooperation/interface between pharmacists and physicians should be considered as well. Additionally, the question of should all patients receive counseling or only have access to counseling based on carefully described criteria must be asked. It may not be cost effective (or necessary) for all patients to be counseled; some clearly will need counseling; all should have counseling available to them on request.

- Page 28; regarding confidentiality - pharmacists already have access to confidential information and this must continue for them to perform their role as required by good standards of care.

- Page 29, second paragraph - excellent.

- Page 29, third paragraph - the availability of the patient's diagnosis or treatable illness would assist immensely with DUR and counseling. Again, the institutional model and that used by the U.S. Indian Health Service in its outpatient clinics could be applicable to your observations.

- Page 30; regarding pharmacist-only access to ECP data system - it appears to me that a necessary goal is to free up pharmacist time from the count and pour and lick and stick aspect of practice (technical functions) so he can spend more time with patients for counseling and DUR. Locking the pharmacist to a CRT display only relegates him to maintaining these technical aspects of his job at the expense of desired clinical interaction with patient and physician. A look at the institutional model, plus activities as currently carried out in community pharmacy, would demonstrate supportive personnel access to this information without compromise of confidentiality.

- Page 31; regarding automated therapeutic review by fiscal intermediaries - these are the wrong parties to conduct such activities. Although they may be "less biased," they don't have the expertise or local perspective. Suggest model similar to Pharmacy and Therapeutics Committees in hospitals be considered using pharmacists and physicians.

- Page 31; regarding assessing performance of participating pharmacists - agreed!

- Page 32; regarding variety of educational interventions - must take time to describe these in specific terms in advance of program implementation.

- Page 33; regarding the blue ribbon panel - not only do DUR standards need criteria, but so do drug use standards.

- Page 34 - programs should be initiated to influence and support both medical school and pharmacy school curricula.

Finally, some references need correcting:

- Page 2 - Dr. Donald T. Rucker
- Page 39; Endnote 59 - Hepler, C.D.
  Endnote 71 - Benjamin Hershenson

You may also wish to contact Dr. Henri R. Manasse, Jr., Dean of the University of Illinois at Chicago College of Pharmacy. Dean Manasse has just completed a public paper on "drug misadventuring" which elaborates on and further clarifies many of the observations appearing in the Report.

Again, thank you for the opportunity to comment on the Report. If we can be of further assistance, please let me know.

OIG RESPONSE TO AACP COMMENTS

The AACP comments provide helpful clarifications and elaborations. We have made some clarifications and revisions in response to them. Most notably, we have amended our recommendation concerning pharmacy counseling to urge that pharmacists in accord with carefully developed criteria assure that all Medicare patients have access to counseling services. Previously, we simply recommended that pharmacists provide counseling services to all Medicare patients.

NATIONAL ASSOCIATION OF BOARDS OF PHARMACY COMMENTS

I am pleased to comment on behalf of the National Association of Boards of Pharmacy (NABP) in regard to the draft report entitled "Medicare Drug Utilization Review." NABP is the national association of the 50 state boards of pharmacy, the District of Columbia, Puerto Rico, the Virgin Islands, some provinces of Canada, and the Pharmacy Board of Victoria, Australia. I, again, would like to commend Dr. Yessian and his staff for the concise and comprehensive review of the subject. We are pleased that the Department of Health and Human Services and the Office of the Inspector General are involving themselves in issues and concerns that have been of interest to pharmacy for some time. An unbiased examination of issues, such as the "Medicare Drug Utilization Review," provides pharmacy regulators and practitioners with a much needed "outside perspective."

The comments offered on behalf of NABP will focus on those findings and recommendations that affect the protection of the public health, specifically, the design and operation of a multilevel DUR effort and the need to develop safeguards to protect the integrity of the Medicare DUR Program. The other issues raised in the report, although important, are not within our scope as the national association for state boards of pharmacy.

Findings

We concur with the report's finding on page 3 that the problem of mismedication in the elderly population is significant. Furthermore, the problem does not seem to be lessening but appears to be increasing as the elderly population grows and the pharmaceutical industry introduces countless "me too" drugs. We agree further that the Medicare Drug benefit program will increase the occurrence of mismedication if it is not effectively implemented and managed.

The report notes on page 5 another serious cause of mismedication in the elderly, polypharmacy; "Because they suffer from multiple chronic diseases, older adults are frequently under the care of more than one physician who may prescribe drugs without knowledge of the patient's full drug regimen." This finding should be an important consideration when developing the Medicare DUR Program. Related to this, but not mentioned in the report, is the issue of physician dispensing. Under the Medicare Catastrophic Coverage Act, physicians are entitled to participate as providers in the drug care benefit program. An effective DUR system should also provide access to the medications dispensed by physicians.

Recommendations

Development of the DUR Program

In the interest of the public health and safety, we agree that attention must be given to design a comprehensive DUR program. "The human costs associated with death, illness and incapacitation among the elderly as a result of mismedication are incalculable." It is imperative that "a comprehensive Medicare DUR program that emphasizes therapeutic as well as program integrity issues" be established.

Design of the DUR Program

Patient Drug Regimen

The report identifies the pharmacist/dispensing level as "the most critical point at which medication errors can be identified and corrected for individual patients." We agree wholeheartedly with this statement and urge the HCFA to develop and design the Medicare DUR program with this in mind. If mismedication can be prevented and controlled at this level significant public health and cost benefits will be realized.

And, if mismedication is to be prevented and controlled, the pharmacist must have access to a patient's drug regimen. We do not believe that the proposed prompts to pharmacists identifying potential ADRS will provide the pharmacist with all of the necessary information to make a decision about a patient's course of therapy. The report affirms this point; "Although a system of prompts to alert pharmacists to potential ADRs would be useful tool and should be included in the data system, it cannot substitute for the judgement made by a pharmacist."

Of course, NABP recognizes that access to a patient's drug regimen raises serious concerns about confidentiality. These concerns should not be ignored. However, we believe that a program can be developed that ensures this confidentiality and provides a mechanism for informed consent from participants.

Nationally Standardized Identification Number

NABP concurs with the report that it is essential for the program to identify providers for the purposes of tracking mismedication problems. We would add that it is also necessary to identify providers for the purpose of ensuring that only qualified and competent providers participate in the program and dangerous or incompetent providers are eliminated or barred from the program.

NABP and the National Council for Prescription Drug Programs (NCPDP) currently maintain a national listing of pharmacies that identifies 97% of all the licensed pharmacies in the United States. Pharmacies are systematically assigned a unique NABP Number by the NCPDP only after verification of licensure in good standing with the appropriate state board of pharmacy or licensing agency. The NABP Number is currently used by pharmacies as an official identifier for licensure and third party reimbursement programs. In some states, the NABP Number is the pharmacy's official license number.

NABP also operates with the state boards of pharmacy a national clearinghouse for pharmacist licensure. Briefly, the disciplinary data bank serves as a central data bank for the state boards of pharmacy. Almost daily, the state boards of pharmacy provide NABP with disciplinary information on the final actions they have taken against the licenses of pharmacists in their states. NABP collates this information (name, license number, states licensed in and state where action was taken) monitors the licensure and disciplinary status of pharmacists, and reports information under secure and confidential conditions to the appropriate state and federal agencies.

The NABP Number and Clearinghouse System would provide HCFA with the mechanisms necessary to protect the integrity of the Medicare DUR System and protect the public from unqualified or dangerous providers. We hope that HCFA will consider utilizing these existing systems rather than unnecessarily expending resources to develop new, duplicative systems.

Fiscal Intermediary/Claims Processing Level

Patient Counseling

NABP agrees with the report on the value and importance of patient counseling. Undoubtedly, it is one of the most effective ways to contain mismedication, not only in the elderly population, but for all patients. However, the quality and quantity of patient counseling required is difficult to define and monitor. The system established to monitor this requirement of the Medicare Drug Program should involve a concerted effort between the boards of pharmacy and appropriate federal agencies utilizing data from the Medicare DUR program. We ask that the HCFA *proceed cautiously i*n this regard and not rely solely or entirely on the fiscal intermediary or ECP data base information.

Patient counseling is an integral part of the practice of pharmacy, which is regulated by the state boards of pharmacy. To create separate federal regulations for one aspect of the practice of pharmacy may be shortsighted and interfere with the responsibilities of the states. Efforts would be better served to create a minimum standard or requirement for patient counseling and work with the state boards of pharmacy to refine state practice acts or rules and regulations to meet the desired outcomes and provide the desired monitoring systems.

NABP is pleased to submit these comments and hope that they will assist the Department of Health and Human Services, the Office of the Inspector General and the Health Care Financing Administration implement a monumental health care program. If you have any questions, please feel free to contact me.

OIG RESPONSE TO NABP COMMENTS

We appreciate the information and clarifications provided by NABP. We agree on the importance of a broadly based dialogue to determine appropriate minimum standards for patient counseling and to attempt to apply these standards to pharmacy practice in general. Research and demonstration efforts can be very helpful in this regard.

PUBLIC CITIZEN HEALTH RESEARCH GROUP COMMENTS

Thank you for the opportunity of reviewing your excellent report on the problems of medicating the elderly and, specifically, the pending issue of Medicare Drug Utilization Review.

It is clear that financial barriers prevent many older adults from obtaining medications which they actually need, but it is just as clear that financial barriers protect many other older adults from prescription drugs which will do them more harm than good. The challenge, then, is to figure out a way to reduce or eliminate the first kind of harmful barrier without causing the damage that would result from the second barrier being eliminated. In addition, for those older adults for whom there are no financial barriers, the current problems in mismedication and overmedication urgently need to be addressed.

We have estimated that two-thirds of prescriptions written for older adults are wrong for one of three reasons:

1. The patient's condition, as with mild hypertension, adult-onset diabetes, mild obesity or similar problems is one for which a non-drug treatment should be tried and will often work.

2. A prescription drug is indicated, but the one prescribed is unnecessarily dangerous. (See *Worst Pills, Best Pills,* for the 104 "do not use" drugs and 183 safer alternatives.)

3. The right drug was prescribed but the dose was too high.

In all three of these circumstances, the situation is set up for preventable adverse drug reactions to occur which make up a large proportion of the estimated $7 billion per year spent on health care costs in the elderly attributable to adverse drug reactions.

We agree with the remedies proposed for better regulation by FDA in requiring the drug companies to do more age-appropriate testing of drugs which are intended largely for older adults and the related issue of better labeling concerning the need to usually lower the starting dose of most drugs for older adults.

But the enormity of the epidemic of mismedication of older adults needs more than better education of new doctors and pharmacists and the collection of doctor and patient-specific prescribing data. Contrary to the views expressed by some, the studies done by Ray, Schaffner and colleagues at Vanderbilt on patterns of misprescribing by doctors using the Medicaid billing data have generated very useful data concerning the small fraction of doctors accounting for a disproportionate amount of the worst kind of prescribing such as the dangerous drug chloramphenicol for trivial infections.

I would strongly support, as your study and the legislative history do, the inclusion of encrypted doctor identifiers in the data which is collected along with encrypted patient identifiers so that problems can be discovered as soon as possible.

On page ten of the draft report, commenting on our book, *Worst Pills, Best Pills,* you state that although this kind of information "is useful in sensitizing older adults and health care professionals to the dangers of mismedication," it "can not substitute for a formal set of guidelines that will ensure improved testing and labeling of medications for the elderly." While agreeing with this, I must add that your report would be more complete if it included a recommendation to restore the important patient prescription drug package insert program which was to have gone into effect for 10 categories of drugs amounting to more than 14% of all prescriptions filled but was cancelled entirely by the Reagan administration in the spring of 1981.

Finally, and omitted entirely in the drug portion of the catastrophic coverage legislation, is the issue of drug formularies, limited lists or similar restrictions on which drugs will be reimbursed for by Medicare. (Aside from the "certain narrow exceptions" referred to in your report, the use of a formulary is prohibited.)

It is true, as it is in many other respects, that Medicaid can hardly be used as a model for limiting the scope of reimbursed drugs. No state Medicaid program, in my view, has begun to place adequate limitations on the large number of drugs which should not be reimbursed or which should only be reimbursed for certain indications. Even if we surprisingly revamped current medical education so that future students and residents had much better training in geriatric pharmacology and prescribing, this would still leave over 90% of the doctors who take care of the elderly without the skills to prescribe intelligently. As one geriatrician said, correctly describing the dangerous current state of affairs, the purpose of a geriatrician is to take older people off of drugs other doctors put them on.

What is thus needed, in addition to reforms in FDA's requirements for drug testing and labeling and improvements in education of health care professionals and older people, is a formulary or restricted list of drugs. With 100% certainty, this will come to pass as it has in the best hospitals in this country, in other health care delivery settings in the U.S and in many foreign countries.

The question is, therefore, not whether it will happen but when, and what needs to be done now to hasten the day when an amendment is passd to the existing drug-coverage legislation for Medicare which requires, rather than prohibits, such a formulary. The present legislation prohibits the use, for reimbursement purposes, of formularies. But within the scope of Drug Utilization Review program objectives is room for studying the usefulness of formularies in improving drug prescribing and as remedies for this epidemic of drug-induced disease and waste of billions of dollars in elderly people. I hope you will make this recommendation.

OIG RESPONSE TO PUBLIC CITIZEN HEALTH RESEARCH GROUP

We appreciate the positive assessment and the supplemental information provided by Public Citizen Health Research Group. We agree that the problem of mismedication of the elderly is quite serious warranting concerted government action. With respect to the additional recommendations called for, we recognize the arguments put forth but feel that our own inquiry does not provide sufficient basis to make the recommendations.

APPENDIX II

ENDNOTES

1. *Prescription Drugs and Elderly Americans: Ambulatory Use and Approaches to Coverage for Medicare,* U.S. Congress, Office of Technology Assessment, October 1987, p. 2.

2. *American Association of Retired Persons Issue Brief,* March 1987; Testimony before Senate Special Committee on Aging.

3. *Prescription Drugs and Elderly Americans,* p. 3-1.

4. Smyer M., "Polypharmacy in the Elderly: Interventions Based on Therapeutic Drug Utilization Review," submitted to Hartford Foundation, June 1988, p. 2.

5. Wolfe S., Fugate L., Hulstrand E., Kamimoto L., *Worst Pills Best Pills* (Washington D.C.: Public Citizen Health Research Group, 1988) p. 7.

6. Ray W., "Prescribing Patterns of Drugs for the Elderly," *Pharmaceuticals for the Elderly* (Washington: Pharmaceutical Manufacturers Association, 1986), p. 35.

7. "Background Papers," *Surgeon General's Workshop: Health Promotion and Aging,* edited by Faye Abdellah and Steven Moore, March 1988, p. E-2.

8. *Prescription Drugs and Elderly Americans,* p. 2-3.

9. Testimony of Helene Lipton, Ph.D., Associate Professor, Division of Clinical Pharmacy, School of Pharmacy, and Senior Research Associate, Institute for Health Policy Studies, School of Medicine, University of California, San Francisco, before the Senate Special Committee on Aging, July 20, 1987.

10. Smyer M., Ahern F., Lago D., Nielson R., "Reducing the Risk of Prescription Drug Interactions and Estimating Risk Prevalence of Prescription Drug Interactions in Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) Program," Final Report submitted to Andrus Foundation of the AARP, December 1987, pp. 3-4.

11. Statement of Dr. Robert Windom, Assistant Secretary for Health, U.S. Department of Health and Human Services, at a press conference announcing, "Priorities and Approaches for Improving Prescription Medicine Use by Older Americans," a report of the National Council for Patient Information and Education, Washington, D.C., October 1987.

12. *Harvard Medical School Health Letter,* July 1986.

13. *Surgeon General's Workshop*, p. E-7.

14. *Worst Pills*, p. 13.

15. Ibid., pp. 14-15.

16. *Senate Special Committee on Aging*, Hearings on Adverse Drug Reactions in the Elderly, 1988.

17. Testimony of Helene Lipton.

18. Southwick K., "A Prescription for Trouble: Drugs to Counteract Drugs," *Health Week*, August 8, 1988, p. 1.

19. Testimony of Thomas Snedden, Director, PACE Program, Pennsylvania Department of Aging, before Subcommittee on Health and the Environment, Committee on Energy and Commerce, May 21, 1987.

20. Speech by Thomas Snedden, presented at seminar, "The Prescription Drug Benefit of the Medicare Catastrophic Coverage Act," sponsored by the Food and Drug Law Institute, July 26, 1988.

21. Statement of Wayne Ray, M.D., Director of Division of Pharmaco-Epidemiology, Vanderbilt University School of Medicine. Printed in *Arizona Republic*, June 26, 1988.

22. Testimony of Peter Lamy, Ph.D., Professor and Director, The Center for the Study of Pharmacy and Therapeutics for the Elderly, University of Maryland at Baltimore, before Senate Special Committee on Aging, July 20, 1987.

23. Similarly, in March 25, 1988 testimony before the Senate Special Committee on Aging, William Simonson, Pharm.D., reported that among the 24 most commonly prescribed drugs for the elderly, only three product labels cite the geriatric patient under "adverse reactions" and only five mention geriatrics under "dosage and administration."

24. Ibid.

25. *Worst Pills*, p. 17.

26. Testimony of William Simonson.

27. Testimony of Jerome Avorn, M.D., Director, Program for the Analysis of Clinical Strategies, Harvard Medical School, before the Senate Select Committee on Aging, March 25, 1988.

28. *Worst Pills*, p. 9.

29. Avorn J., Soumerai S., "Improving Drug Therapy Decisions Through Educational Outreach," *New England Journal of Medicine,* 308, no. 24, p. 1458.

30. Statement of Dr. Robert Butler, Director of Department of Geriatrics, Mt. Sinai Hospital and former Director of the National Institute for Aging, U.S. Department of Health and Human Services. Printed in *Arizona,* June 29, 1988.

31. Schneider E.L., William T.F., "Geriatrics and Gerontology: Imperatives in Training and Education," *Annals of Internal Medicine,* 104: 3, March 1986, pp. 432-435.

32. Ibid.

33. *Technology and Aging in America,* U.S. Congress, Office of Technology Assessment, June 1984.

34. Brater C.D., Nierenberg D.W., "Medical School Education in Clinical Pharmacy and Therapeutics," and "Improving Medical Education in Therapeutics, "*Annals of Internal Medicine* 108: 1, January 1988, pp. 136-145.

35. Gottlieb R.M., Nappi T., Strain J.J., "The Physician's Knowledge of Psychotropic Drugs: Preliminary Results," *American Journal of Psychiatry,* 135: 29, 1978.

36. Weiner J., Schumacher G.E., "Psychotropic Drug Therapy: Knowledge of Health Care Practitioners," *American Journal of Hospital Pharmacy,* 33: 237, 1976.

37. Biron P., "A Hopefully Biased Pilot Survey of Physicians' Knowledge of the Content of Drug Combinations," *Canadian Medical Association.*

38. Ferry M.E., Lamy P., Becker L., "Physicians' Knowledge of Prescribing for the Elderly, " *Journal of American Geriatrics Society,* 33: 616, 1985.

39. Testimony of William Simonson.

40. Carruthers S.G., "Clinical Pharmacology of Aging," in *Fundamentals of Geriatric Medicine,* (Raven Press, 1983).

41. Testimony of Ms. Wilda Henry before the Senate Special Committee on Aging, March 25, 1988.

42. Testimony of Ms. Ann Little before the Senate Special Committee on Aging, March 25, 1988.

43. Avorn J., Chen M., Hantley R., "Scientific Versus Commercial Sources of Influence in the Prescribing Behavior of Physicians," *American Journal of Medicine,* 73, July 1982.

44. *Advertising Age,* January 1988.

45. Silverman M., Lee P.R., *Pills Profits and Politics,* (Berkeley, California: University of California Press, 1974) pp. 54-57.

46. Statement of Mark A. Stratton, Project Director, Geriatric Education Center, University of New Mexico. Printed in *Arizona Republic,* July 1, 1988.

47. Ross S., White S., Hogan L., Godwin H., "The Effect of a Mandatory Patient Counseling Regulation on the Counseling Practices of Pharmacy Practioners," *Contemporary Pharmacy Practice*, 4:2, 1981, p. 64.

48. *Survey of Pharmacy Law*, National Association of Boards of Pharmacy, 1988, p. 34.

49. Kirking D.M., "Pharmacists' Perceptions of Their Patient Counseling Activities," *Contemporary Pharmacy Practice,* 5, 1982, pp. 230-238.

50. Kimberlin C., "Communications," chapter in Wertheimer A.I., Smith M.C., ed, *Pharmacy Practice: Social and Behavioral Aspects,* vol. 2, in press.

51. Puckett F.J., White S.J., Mossberg H.E., Matchett J.A., "Pharmacist/Patient Counseling Practices," *Contemporary Pharmacy Practice*, 1, 1978, pp. 67-71.

52. Mason H.L., Svarstad B.L., "Medication Counseling Behaviors and Attitudes of Rural Community Pharmacists," *Drug Intelligence and Clinical Pharmacy*, 18, 1984, pp.409-414.

53. Svarstad B.L., Mason H.L., "Factors Affecting the Pharmacist's Consultation Behavior: A Multivariate Study," Communication Paper presented at AACP annual meeting, Denver, July 1979.

54. Communications, p.9. Refers to Dickson W.M., Rodowskas C., "Verbal Communications of Community Pharmacists," *Medical Care,* 13, 1975, pp. 486-498.

55. "Effect of Mandatory Patient Counseling".

56. Smith M.C., Sharpe T.R., "A Study of Pharmacists' Involvement in Drug Use by the Elderly," *Drug Intelligence and Clinical Pharmacy,* 18, 1984, 525-529.

57. Morris L.A., "A Survey of Patients' Receipt of Prescription Drug Information," *Medical Care,* 20, 1982, pp. 596-605.

58. Ibid.

59. Hepler C.D., "Unresolved Issues in the Future of Pharmacy," *American Journal of Hospital Pharmacy,* 45, 1988, p. 1071.

60. Ibid. p. 1073.

61. Gerber K., Nehemkis A., *Compliance: The Dilemma of the Chronically Ill* (New York: Springer Publishing 1986), p. 131.

62. Christensen D. "Drug Taking Compliance: A Review and Synthesis," *Health Services Research,* Summer 1978, p. 176.

63. Marston M. "Compliance with Medical Regimens: A Review of the Literature," *Nursing Research,* 19:4, 1970, p. 317.

64. Blackwell B., "The Drug Defaulter," *Clinical Pharmacology and Therapeutics,* 13:6, 1972, 841-848.

65. Ibid.

66. "Drug Taking Compliance" p. 176.

67. *Compliance: The Dilemma,* p. 133.

68. Survey conducted by Office of Inspector General, Office of Analysis and Inspections, 1988.

69. "The Minnesota Medicaid Program: An Overview," Minnesota Department of Public Welfare, 1988.

70. "Reducing the Risk."

71. Discussions with panel of experts convented in August 1988 by OIG, OAI, Region I. Guests: Jerome Avorn, M.D., Director, Program for the Analysis of Clinical Strategies, Harvard Medical School; Benjamin Hershenson, Dean, Massachusetts College of Pharmacy; Ronald Jordan, Vice President, Blue Cross.

72. Ibid.

73. Evans E., Haynes R., Birkett N., Gilbert J., Taylor D., Sackett D., Johnston M., Hewson S., "Does a Mailed Continuing Education Program Improve Physician Performance," *Journal of American Medical Association,* 255:4, p. 503.

74. Avorn J., Soumerai S., "Improving Drug Therapy Decisions Through Educational Research," *New England Journal of Medicine,* 308:24, June 1983, pp. 1457-1463.

223 L

75. Soumerai S., Avorn J., "Economic and Policy Analysis of University Based Drug Detailing," *Medical Care,* 24:4, April 1986, p. 313.

76. Ray W., Schaffner W., Federspiel C., Miller W., "Improving Antibiotic Prescribing in Office Practice," *Journal of American Medical Association,* 250:13, pp. 1728-1733.

77. Ibid.

78. Smith M., Garner D., "Setting A Value on Patient Counseling," *U.S. Pharmacist,* August 1987, pp. 12-19.

79. Discussions with William Thien, Vice President for Health Services, Walgreen Drug Corporation, August and September 1988.

80. Knapp D.A., Wolfe H.H., Knapp D.E., Rudy T.A., "The Pharmacist As Drug Advisor," *Journal of the American Pharmaceutical Association,* NS9:10, 1969, p. 502.

81. Campbell R.K., Grisafer J.A., "Compliance with the Washington State Patient Information Regulation," *Journal of the American Pharmaceutical Association,* NS15, 1975, p. 494.

82. Mason H.L., "Using Attitudes and Subjective Norms to Predict Pharmacist Counseling Behaviors," *Patient Counseling and Health Education,* 4, 1983, pp. 190-196.

83. Beardsley R.S., Johnson C.A., Wise G., "Privacy As A Factor In Patient Counseling," *Journal of the American Pharmaceutical Association,* NS 17, 1977, pp. 366-368.

84. Walkins R.L., Norwood G.J., Meister F.L., "Improving the Quality of the Pharmacist as a Drug Advisor to Patients and Physicians through Continuing Education," *American Journal of Pharmaceutical Education,* 40, 1976, pp. 34-39.

85. "Unresolved Issues."

86. Discussions with staff of the Hartford Foundation, New York, currently funding demonstration projects related to pharmacist counseling of elderly patients.

87. Ascione F., Shimp L., "The Effectiveness of Education Strategies with the Elderly," *Drug Intelligence and Clinical Pharmacy,* 18, November 1984, pp. 926-931.

88. Wandless L., Davie J.W., "Can Drug Compliance in the Elderly Be Improved," *British Medical Journal,* February 5, 1977, pp. 359-361.

89. Barbagallo-Sangiorgi G., *Aging and Drug Therapy* (New York: Plenum Press, 1984), p. 58.

90. Hammarlund E., Ostrom J., Kethley A., "The Effects of Drug Counseling and Other Educational Strategies on Drug Utilization of the Elderly," *Medical Care*, 23:2, pp.165-170.

91. Ibid., p. 165.

92. Expert Panel.

93. Worst Pills.

94. Smith M., "The Cost of Non-Compliance and the Capacity of Improved Compliance to Reduce Health Care Expenditures," *Improving Compliance: Proceedings of a Symposium,* National Pharmaceutical Council, Washington D.C., November 1984, pp. 35-44.

95. Joyner T.L., Fikrat H.T., Catania P.N., "Evaluation of a Medication Service for Geriatric Patients in a Congregate Housing Facility," *American Journal of Hospital Pharmacy,* 40:9, 1983, p. 1509.

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SELECT COMMITTEE ON AGING

April 21, 1989

Dr. Frank E. Young
Commissioner
Food and Drug Administration
Room 14-71 Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

I would like to take this opportunity to thank you for appearing as a key witness at our hearing held on Wednesday, April 19 entitled, "Drug Misuse Among the Elderly and Its Impact on Community Based Care."

Your testimony was extremely important to the Subcommittee, and it was a pleasure to have you appear before us. The hearing was a great success, and your comments and concerns were very helpful to the Subcommittee as we continue to monitor the growing problem of drug misuse among our growing elderly population. I was very glad to hear that the guidelines for premarket clinical testing of drugs on the elderly will be ready for publication in the very near future, and I urge you to continue to expedite their completion. I would appreciate being kept up to date on their progress.

The issue of drug misuse among the elderly is of great importance to this Subcommittee, and we will be planning follow-up activities on this subject in the very near future. I will be sure to keep you informed of our plans.

Once more, I thank you for being with us last week. I look forward to hearing from you soon.

With best wishes, I am

Sincerely,

THOMAS J. DOWNEY
Chairman
Subcommittee on Human Services

TJD:mb

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 25 1989

The Honorable Thomas J. Downey
Chairman, Subcommittee on Human
Services
Select Committee on Aging
House of Representatives
Washington, D.C. 20515

Dear Mr. Downey:

This is in response to your April 21, 1989 letter to Dr. Frank E. Young, Commissioner of the Food and Drug Administration, concerning the guideline for premarket clinical testing of drugs on the elderly. You asked to be kept informed of our progress in completing the guideline.

At this time a draft of the guideline is being circulated internally for review. As soon as the guideline is completed and the Agency is ready to announce its public availability, we will let you know and provide the Subcommittee with a copy. As Dr. Young indicated during your April 19 hearing, we expect this process to require about six months to complete.

We hope this information is helpful. If we can be of any further assistance, please let us know.

Sincerely yours,

Hugh C. Cannon

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

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May 15, 1989

Dr. Frank E. Young
Commissioner
Food and Drug Administration
Room 14-71 Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

As a follow up to your testimony before our Subcommittee on Human Services on April 19 on Drug Misuse Among the Elderly and Its Impact of Community Based Care, I would appreciate your looking over the following pages and supplying the Subcommittee with the corresponding items. These will be included in the official hearing record, which we hope to send to the printer soon.

On page 47, you refer to the visual which was of great interest to the Subcommittee during your testimony. This visual was in the form of a chart that contained important percentages and numbers. Would it be possible for your staff to supply this chart in a reduced form for inclusion?

On page 49, you read a portion of an article that appeared in the Journal of American Geriatric Society which discussed how the incidence of adverse reactions increases with the number of drugs taken. Would it be possible to get a copy of that article?

You discuss, on page 51, the analysis of data to determine differences in toxicity as part of the clinical and statistical guideline that was finalized in 1988. Below that you indicate that the guideline is being submitted for the record. To date, we have not received a copy of that guideline, and we think it is important to have.

On page 52, you indicated that you would supply us, from your rough notes, with a table which would outline pharmacokinetic differences. This would be an excellent addition for the hearing record.

You mention, on page 54, 500 leaflets you have distributed through AARP on patient information. Would it be possible to receive a copy of this brochure?

Additionally, on page 55, you mention that you will submit for the record an article on medical education response in the 20th century. The Subcommittee would appreciate receiving that article for inclusion.

Page 60 contains a reference you made to an article of Nolan and quotes as well. Would it be possible to have that article?

You mention a consumer report on page 67. Is this report available for the hearing record?

I took the liberty of asking you some questions about the training of students at medical schools which appear on pages 65 through 68. You indicated at that time you would be happy to respond at a later date. Would you be able to respond now?

Finally, on page 70 you discuss good models of schools that have geriatric training programs and/or centers on aging. The Subcommittee would like to have those models listed in the hearing record.

I appreciate your cooperation in responding to the previous questions as soon as possible. We would like to send the completed transcript into the printer no later than May 30. If you have any questions or require additional information, please do not hesitate to call me or my staff at 226-3348.

With best wishes, I am

Sincerely,

THOMAS J. DOWNEY
Chairman

TJD:mb
Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 1 1989

The Honorable Thomas J. Downey
Chairman, Subcommittee on Human Services
Select Committee on Aging
House of Representatives
Washington, D.C. 20515

Dear Mr. Downey:

This is in partial response to your May 15, 1989 letter requesting several items to be included in the official record of the Subcommittee's hearing on April 19. We will provide the remaining items as soon as they are available. The following items are listed in the same order as described in your letter:

1. You describe a visual (page 47 of the hearing transcript) presented during the testimony, as containing "important percentages and numbers." The visual Dr. Young presented had no numbers; it merely symbolized the "cornerstone of optimal drug therapy" in the form of a pyramid, with the three bases identified as "informed patient," "informed educated physician," and "properly labeled safe and effective drugs." We regret that we do not have a reduced form of this visual.

2. Enclosed is a copy of an article from the Journal of American Geriatrics Society, discussing the "incidence of adverse reaction increases with the number of drugs taken." (Prescribing for the Elderly, Part I: Sensitivity of the Elderly to Adverse Drug Reactions: Lisa Nolan, BS (Pharm), MS, and Kevin O'Malley, M.D., PH.D. JAGS 36:142-149, 1988)

3. Enclosed is a copy of the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications which was mentioned on page 47 of the transcript.

4. Enclosed are several examples of Medication Information Leaflets for Seniors (MILS) which Dr. Young mentioned during the hearing (page 54 of the transcript). Over 93 MILS have been co-written by FDA for the American Association of Retired Persons (AARP); since many of the MILS apply to classes of the drugs and not just to individual drug entities, the actual number of products they cover is much greater than 93.

5. The Nolan article referenced on page 60 of the hearing transcript is the same article described in item two above.

6. Enclosed is a copy of the current "Status Report on Patient Education Activities" which was referenced on page 67 of the transcript.

We hope this is helpful.

Sincerely yours,

Hugh C. Cannon

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

Enclosures

Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION

July 1988

For further information regarding the clinical aspects of the guideline please contact:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I (HFD-100)
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-4330

For further information regarding the statistical aspects of the guideline please contact:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Epidemiology and Biostatistics
Division of Biometrics
Statistical Evaluation and Research Branch (HFD-713)
5600 Fishers Lane
Rockville, Maryland 20857
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GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION

I. INTRODUCTION

This guideline is intended to assist an applicant in presenting the clinical and statistical data required as part of an application under 21 CFR 314.50. The guideline describes an acceptable format for organizing the clinical and statistical sections and presenting the clinical and statistical information and accompanying statistical documentation of a clinical trial. With respect to documenting the results of individual studies, the guideline describes a fully integrated clinical and statistical report rather than two separate reports.

Paragraphs (d)(5), (d)(6), and (f) of 21 CFR 314.50 provide a general outline for this submission:

Clinical Section [21 CFR 314.50(d)(5)]

A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

(vi) A summary and updates of safety information, as follows:

(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(b) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports (1) 4 months after the initial submission; (2) following receipt of an approvable letter; and (3) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50.

Statistical Section [21 CFR 314.50(d)(6)]

A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5)(ii) of this section concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5)(vi)(a) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

(Although the regulations do not call for submission as part of the statistical section of information described under paragraph (d)(5)(v), this was an error and the integrated summary of effectiveness data (Section II.G) should be included.)

Case Report Forms and Tabulations [21 CFR 314.50(f)]

The archival copy of the application is required to contain the following case report tabulations and case report forms:

(1) Case report tabulations. The application is required to contain tabulations of the data from each adequate and well-controlled study under section 314.126 (Phase 2 and Phase 3 studies as described in section 312.1(a)(2) [designated sections 312.21(b), (c) in a subsequent revision of regulations, Form FDA-1571], tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in section 312.1(a)(2), Form FDA-1571), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the application. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the application, in accordance with paragraph (f)(3) of this section.

(2) Case report forms. The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

(3) Additional data. The applicant shall submit to FDA additional case report forms and tabulations needed to conduct a proper review of the application, as requested by the director of the FDA division responsible for reviewing the application. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under section 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally. (The preamble to the final regulation notes that every attempt will be made to request additional case report forms within 30 days of receipt of the application.)

(4) Applicants are invited to meet with FDA before submitting an application to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in a form other than hard copy, for example, on microfiche or machine readable formats.

In addition to 21 CFR 314.50, several other sections of the regulations bear directly on the contents of the clinical section of the application:

1. Adequate and Well-Controlled Studies. 21 CFR 314.126 describes the characteristics of a study the agency considers in determining whether a study is adequate and well-controlled and thus can contribute to the "substantial evidence" needed for approval.

2. Refusal to Approve the Application. 21 CFR 314.125 lists the reasons, many of them related to the results reported in the clinical data section, that would cause the agency to refuse to approve an application.

3. Fixed Combinations. 21 CFR 300.50 describes the particular requirements applicable to a combination drug product.

4. Labeling. 21 CFR Part 201 describes the contents of drug labeling.

This guideline supplements and expands the general outline provided in the regulations. Because it must remain broad enough to apply to all drug classes, it deals with the topics and kinds of displays and analyses that should be considered by any applicant, and how to organize them, rather than with the specific data requirements for approval of a specific kind of drug. Guidance regarding such specific data requirements can be found in FDA's clinical guidelines, including both the "General Considerations for the Clinical Evaluation of Drugs" and the many guidelines dealing with the evaluation of individual drug classes.

The guideline is directed principally toward an application for a new molecular entity, i.e., an agent not previously marketed in the United States in any dosage form. While many parts of it are equally applicable to other applications (e.g., Section III, The Format and Content of the Full Integrated Clinical and Statistical Report of a Controlled Clinical Study, is useful for presenting any well-controlled study in support of an effectiveness claim), others are not. For example, it would not be necessary to include safety data already contained to in a previously approved application in an application for a different dosage form, new salt or ester, new combinations or new claim.

The objective of this guideline is to help applicants prepare a submission of the clinical and statistical sections that is complete and easily reviewable, that contains most of the summary and basic data that will be needed for evaluation, and that organizes and presents the data and analyses in a manner that is as clear, transparent, unambiguous, and accessible as possible. A lucid, well-organized, well-displayed, and complete application helps a reviewer become quickly oriented to its contents, facilitates examination of the relationships in the data that are of interest, and allows the reviewer to move easily between basic data and analyses and summary tables or verify reported results of analysis by duplicating them or carrying out alternative analyses. The guideline provides particularly extensive guidance on three critical aspects of the submission of clinical and statistical data.

1. The overall organization of the clinical and statistical sections, i.e., where, and in what order, to present and cross-reference descriptions and analyses of the clinical studies, overall analyses, etc., is provided in Section II.

2. How to present data from an individual study, including the aspects of the protocol and conduct of the study that should be presented and discussed, the effectiveness and safety data to be displayed and how much individual data to present in the study report, and the contents of supplementary tabular listings, is explained in section III.

3. The integrated overall analyses that take data from groups of studies to provide an overview of effectiveness and safety that is broader than that of a single trial are described in Section II. The integrated summary of effectiveness is in Section II.G; the integrated summary of safety is in Section II.H.

Several principles have shaped development of this guideline:

1. It is important to distinguish presentation of data from the subsequent evaluation, interpretation, and analysis of those data, because the two uses of data require different treatment. Data presentation should involve relatively little judgment or selection, other than that devoted to assuring effective data display. Thus, presentation of the results of a study should include all patients, all time points, and all endpoints, unless there has been prior indication by the agency that a particular subset of these data should be the only one considered. Similarly, reported adverse events should be presented whether they are perceived as intercurrent illness, reactions to other therapy, part of the natural history of the disease being treated, conditions present at baseline that worsened or truly related to use of the test drug. Moreover, all studies initiated, whether completed or abandoned, should be presented in sufficient detail for a reviewer to comprehend their design and outcome. On the other hand, once the data are presented in full, the interpretation and analysis of the data, and the conclusions reached, necessarily involve selection, judgment, and explanation.

2. Interrelationships among data from different studies should be examined; i.e., studies cannot be considered only in isolation. One consequence of this is rejection, for purposes of format, of the concept of the "pivotal" study, which has all too often been nothing more than the one or two of a group of similar studies that worked out best. Studies should be grouped by design and, within design, by other relevant features, such as whether case records are available and where the study was carried out. The implications of all studies, successful, non-supportive, terminated, etc., need to be considered. Differences in results may suggest differences in response among patient populations, inappropriate dose or dose interval, or may have other explanations, or be inexplicable; they do, however, warrant attention. Of course, it remains important for the sponsor to identify those studies believed to fulfill the statutory requirement for adequate and well-controlled studies supporting effectiveness.

A second consequence of this principle is that summaries are called for at a variety of levels, ranging from the broadest (overall summary, integrated summary of effectiveness data, integrated summary of safety information) to more narrow summaries (summary of clinical pharmacology studies). Further, various cross-study analyses are requested, using the larger numbers of patients available in the entire NDA to look for demographic or other features that may influence effectiveness or safety, but that cannot be detected in the individual studies.

3. Studies reported in the literature should be incorporated into appropriate sections of the submission, not treated as an isolated body of data to be placed in a separate category. Published reports should be placed in the various sections of the application in accordance with the kind of data described in the reports. The reports should be discussed and analyzed as their quality and substance dictate.

4. For most analyses, tabular listings, not case report forms, are the "raw data." The revised regulations emphasize the use of tabular listings of data as the "raw data" for review, in lieu of the case report forms (CRF's). The CRF's are used to collect information on each patient studied, but they are often not the best document to use in examining the results of a study. When a particular patient's overall course is of interest, as in the case of a death or serious ADR, or a patient who had a dramatically better response to treatment than other patients, the case report form, or some single patient oriented document derived from the CRF, is the best source of information. Where the responses of a group (patients in one study or patients in a group of studies) for a single effect (e.g., blood pressure) or several effects (e.g., blood pressure, heart rate, serum potassium, and serum uric acid) are of interest, a tabular listing of patients and their results allows easy examination of the overall results of the individuals in the group for a single measurement or for a group of measurements. This also allows for ready identification of missing data elements, outliers, etc. It is also possible to examine effects in relation to demographic, historical, or other features, using data organized with a variety of data elements in the columns (patients are the rows).

   FDA's experience with tabular presentations is extensive, but it does not suggest an advantage to our specifying a particular approach or display. Appendix A provides illustrations that may assist sponsors, but these should be viewed as examples, not required formats and should be modified as situations require. Sponsors are strongly encouraged to be creative and to consult with reviewing divisions on how to make tabulations most informative and useful.

5. The data base behind a table or figure must be readily ascertained. At many points in this guideline, tables or figures are suggested as useful in data presentation. It is critical that for any table or figure there be clear identification of the data set analyzed, clear identification of what is being displayed through use of good headings, identification of units, and labeling of graph axes, and a clear statement in the accompanying text concerning any conclusions drawn from the table.

Although virtually all of the information called for in this guideline has been part of many applications in the past, and much of it has been specifically discussed under previous regulations, including the form 356h and optional expanded summary, the guideline does provide a more defined format for the application and calls for specific new analyses, data displays, and summaries. Although the guideline reflects the experience and best advice of many FDA staff reviewers and managers and draws on a proposal of some years ago by a working group of the Pharmaceutical Manufacturers Association, it will undoubtedly require refinement as attempts to use it suggest the need for additions, deletions, and other changes. If the guideline is to have its intended effect, it must be "user-friendly," i.e., easily understood, flexible enough to fit most applications, free from requests for unnecessary material yet comprehensive enough to include needed data and analyses and minimize need for supplementary submissions. Only attempts to work with it can adequately elucidate its virtues and flaws.

As is true for any guideline, this guideline for the clinical and statistical sections of an application describes one way, but not the only way, of satisfying regulatory requirements. It will undoubtedly be less appropriate in some instances than others and is not intended to inhibit an applicant's search for the best way to exhibit the data and information needed for approval of an application. Nonetheless, it should be appreciated that under 21 CFR 314.101 the Agency can, and intends to, return to applicants (i.e., refuse to file) those applications that are not sufficiently complete or well-organized to permit a substantive review. Attention to this guideline should help sponsors prepare a complete and reviewable document.

II. OVERALL FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS [21 CFR 314.50(d)(5) and (6)]

The clinical and statistical sections [21 CFR 314.50 (d)(5) and (6)] should, in general, be organized following the format and sequence described below. Parts not applicable to a particular application should be omitted (but see discussion of index in Section VI.E.). The following outline includes, in many cases, some description of the specific content of each section, alternative ways of presenting data, or general comments. Note that a description of the Full Integrated Clinical and Statistical Report of a Controlled Clinical Study is given in Section III and that a complete topical outline of the Clinical and Statistical sections of the application is given in Section VI.

A. List of Investigators and List of IND's and NDA's

A complete alphabetical list should be provided of all investigators supplied with the drug substance or drug product by the applicant or known to have investigated the drug, using any dosage form (e.g., on the basis of published or unpublished reports), including the full name and post office address and, after each name, the kind(s) of studies carried out, the study identifier(s), and the location (Volume, page reference) of the description of each study, case report tabulations, and case report forms, if any. Investigators who carried out studies of a dosage form that is not the subject of the application and that is already marketed in the United States may be omitted.

In addition, a list should be provided of all known IND's under which the drug, in any dosage form, has been studied and any other NDA of which the applicant is aware that has been submitted for the same drug substance.

The unexplained omission of any report of investigations made with the new drug by, or on behalf of, the applicant, or of any pertinent reports of clinical experience received or otherwise obtained by the applicant from published literature or other sources, may constitute grounds for refusing to approve the application [(21 CFR 314.125(b)(14)]. Studies of a dosage form that is not the subject of the application and that is already marketed in the United States need not be included.

B. Background/Overview of Clinical Investigations

The general approach and rationale used in developing clinical data should be described in narrative form, including a description of the following areas, as appropriate (but not necessarily in the order listed).

1. How information about the drug derived from the clinical pharmacology studies led to critical features of the clinical studies (starting and maximum dose-interval, kind and frequency of monitoring, titration procedures, etc.).

2. The basis for the critical design features of the clinical trials, such as numbers of patients involved, patient selection criteria, duration of studies, choice of type(s) of control for controlled studies (placebo, active), and a discussion of their suitability, ethical constraints leading to a particular choice, etc., and selection of major clinical endpoints.

3. Reference to existing FDA drug-class clinical guidelines and the General Considerations guideline, explaining any important differences between guideline recommendations and the actual study plan. For example, the sponsor may consider the guideline outmoded or superseded by new or better information, as would be indicated by particular FDA Advisory Committee recommendations or FDA decisions on other agents, or the sponsor might simply believe he has developed a superior or equally satisfactory plan, based on his own expertise or discussions with expert consultants. The clinical guidelines are guidelines, not rules, and need not necessarily be followed. However, divergences from the guidelines should be addressed.

4. Reference to any FDA/sponsor discussions of major issues, such as an end of phase 2 conference, and a discussion of any agreements reached and any important differences between those agreements and the ultimate conduct of the NDA.

5. Selection of areas of special interest for study and analysis, such as studies in elderly or pediatric populations, studies in particular clinical environments, or particular drug-demographic or drug-drug interactions studied prospectively or examined retrospectively through evaluation of phase 3 data.

6. Particular effectiveness or safety issues raised by other drugs of the same pharmacologic or therapeutic class, such as withdrawal effects, important adverse effects (including long-term effects), or important drug-drug interactions, as suggested in the literature or by other data.

7. Specific questions raised by the results of clinical trials or by experience with related drugs and not answered by the clinical trial program. The status of such questions should also be described, for example:

    - to be answered by ongoing studies or studies to be planned, noting particularly those questions for which additional data are anticipated while the application is under review.

- can only be answered by post-marketing surveillance.
- question recognized but no planned evaluation.

This section should include a discussion of any planned evaluation of additional potential indications, such as those approved for related drugs but not yet evaluated for the drug that is the subject of the application, as well as uses of the new drug or related drug that are fairly widespread but not approved for any agent.

C. Clinical Pharmacology [21 CFR 314.50(d)(5)(i)]

1. Types of studies to be included in this section are:

   a. Studies of absorption, distribution, metabolism, and excretion (ADME studies). The full reports of bioavailability and pharmacokinetic studies are included in the Human Pharmacokinetic and Bioavailability Section [21 CFR 314.50(d)(3)], but the Clinical Pharmacology section should summarize those results, emphasizing findings of particular importance to the design of clinical trials, the basis for dosage selection, and optimal use of the drug. The section should include investigations of drug-drug interactions (effects on the pharmacokinetics of the new drug by another drug or on the pharmacokinetics of any other drug by the new drug) and investigations of effects of other diseases or conditions (renal disease, hepatic disease, hypochlorhydria) or demographic characteristics (age, race, sex) on pharmacokinetics. Pharmacokinetic implications of blood level determinations carried out during controlled or uncontrolled trials, including phase 3 "pharmacokinetic screen" measurements, should be considered in this section.

   b. Pharmacodynamic dose range and dose-response studies including:

      1) Early dose-tolerance studies
      2) Short-term studies of therapeutic response or of a principal pharmacodynamic effect thought to relate to therapeutic response (e.g., effects of a beta blocker on heart rate during exercise), including dose response and blood-level response studies.

   c. Studies of pharmacodynamic properties of the drug in humans other than the specific property thought to relate to clinical effectiveness, such as:

      - hemodynamic studies
      - electrophysiologic studies
      - studies of effects on renal function

- studies of effects on G.I. motility or gastric acid secretion
- studies of effects on the immune response
- studies of autonomic effects
- studies of endocrine effects
- studies of CNS effects, such as sedation or impairment of driving ability
- studies of effects on coagulation

d. "Special studies," defined here as all clinical pharmacologic studies not described above. Clinical studies intended to demonstrate the effectiveness and/or safety of the drug should not be included here.

2. Format/content

The following information should be presented in this section:

a. A table of all studies, grouped by the study types described above and, within type, as preferred by the sponsor. The table should list investigators, provide study identifiers (including protocol number and publication citation, if any), give the starting date of the study, give the location in the application of the full report of each study (if the study is both a clinical pharmacology and effectiveness trial, it will need to appear in more than one location; in that case the location of all reports involving the study should be included), tabulations, and case report forms, if any, and give the number, age range, and sex distribution of subjects, study design (randomized, double-blind, parallel, crossover, etc.), the specific formulation and dosage strength used, the control treatment, if any, and the dose range, dose regimen, and duration of dosing. See Table 1 in Appendix A for an illustration of such a table.

b. For each group of studies:

1) A brief synopsis, one to two pages in length, of each study within the group describing the study population and results, including critical numerical data. A narrative description of the outcome without numerical data or a statement only of the "statistical significance" of an effect is not useful. The use of tables is crucial to efficient presentation. Abstracts commonly prepared for scientific meetings illustrate how a description of a study and a reasonable display of critical data can be presented in a small space, but the extreme brevity and very extensive use of abbreviations common to these documents is unnecessary here and should be avoided.

2) A full report of each study, except that human pharmacokinetics and bioavailability studies included under 21 CFR 314.50(d)(3) need not be represented in full here and may be summarized. The synopsis called for in the previous paragraph may be sufficient if it includes critical pharmacokinetic parameters and appropriate graphical representations. Section III below describes the data that should be included in a full integrated clinical and statistical report of a controlled study but the description must be adapted to suit the particular case. If the clinical pharmacology study is a well-controlled trial that is important to the evaluation of the application, it deserves the complete analysis. In many cases, these studies are not so rigorously designed and can be described more briefly. The report should reference the volume and page numbers where the additional tabulations [21 CFR 314.50(f)(1)] and case report forms, if any, are located.

   The report should include a statement [314.50(d)(5)(ix)] that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

3) An overall summary and evaluation of each group of studies, including a brief narrative or tabular comparison of the results of the human studies with the animal pharmacology and toxicology data. Particular attention should be paid to important animal findings not confirmed in humans or human findings not suggested by animal studies. Comparative ADME study results should be incorporated into evaluations of the relationship between animal and human pharmacology and toxicology findings.

c. An overall summary of the clinical pharmacology data, emphasizing findings especially relevant to clinical use of the drug, such as dose-response or blood level response data, duration of action data, and potential problems that could be associated with the observed patterns of metabolism or excretion (e.g., high first-pass effect, dependence on renal function, etc.). While the main pharmacologic effects are of greatest interest, other pertinent properties of the drug identified from human or animal studies should also be discussed. For example, vasodilation, ECG effects, sedation, effects on seizure threshold, and anticholinergic effects would always be pertinent. Documented or potential age-related effects should be highlighted.

D. Controlled Clinical Trials [21 CFR 314.50(d)(5)(ii) and (6)(i)]

The presentation of results of controlled clinical trials should be included in both the clinical and statistical sections.

1. Overview

a. Adequate and well-controlled studies

Approval of a new drug requires substantial evidence of effectiveness. Substantial evidence is defined under the Federal Food, Drug, and Cosmetic Act as "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." The studies presented in this section thus are those that will be used to determine whether there is substantial evidence that the drug is effective.

The requirement for well-controlled clinical investigations has been interpreted to mean that the effectiveness of a drug should be supported by more than one well-controlled trial and carried out by independent investigators. This interpretation is consistent with the general scientific demand for replicability. Ordinarily, therefore, the clinical trials submitted in an application will not be regarded as adequate support of a claim unless they include studies by more than one independent investigator who maintains adequate case histories of an adequate number of subjects.

There have, however, been instances in which a single particularly persuasive study has been accepted in support of a claim because the study was considered unrepeatable on ethical grounds. In the case of the approval of timolol for reduction of post-infarction mortality, for example, a major effect on mortality was demonstrated in a single study. The timolol study was very persuasive because of excellent design, minimal or no problems during execution of the study, and a high degree of statistical significance associated with the critical finding. Such cases are unusual and an applicant seeking to invoke these exceptional circumstances must provide strong support for this position.

In general, a study for which case reports are not available will not be relied upon as a well-controlled study contributing to substantial evidence of effectiveness. Special circumstances have permitted exceptions to this policy, especially when such a study is used to support at least one other study with fully available case records. Extreme rarity of a disease, for example, may argue for reliance on published data collected over a long period, even if case records cannot be obtained, when comparable data could not be assembled prospectively in well-controlled studies over a reasonable time. In addition, when a drug is already approved for a major claim, secondary claims have sometimes been approved based on published data. When published studies are used as support for a claim, they should be analyzed in light of the reporting requirements for a study set forth below in Section III.

b. Combination drug products

If a drug product is a fixed combination, the adequate and well-controlled studies requirement applies to those studies intended to show that each component of the combination contributes to the claimed effect. (See 21 CFR 300.50 for the complete regulation on combination drug products.)

c. Submission of all data

All controlled clinical studies, including incomplete or abandoned studies, and all pertinent data, whether developed with support of the sponsor or obtained from any other source should be presented in this section. For any study intended to support effectiveness the discussion of each study should include the full report described in Section III, but in others an abbreviated report omitting some of the details of study design and effectiveness analyses will be sufficient [See II.D.2.c.5)].

The regulation is perhaps ambiguous on where to present a controlled trial available to the sponsor only as a report in the literature, i.e., in the section on controlled trials or in the "other information" section, but it seems best to include all controlled trials pertinent to the claimed effects of the drug in the controlled trials section. Although the absence of case records, an original protocol, and other information would ordinarily limit reliance on these studies, they should be considered as part of the available controlled data base.

2. Format/content

   The following information should be presented:

   a. A table of all studies included, grouped as described below. The table should list investigators, provide study identifiers (including protocol number and publication citation, if available), give the starting date of the study, give the location in the application of the full report of each study and its tabulations and case report forms, if any, and give the number, age range, and sex distribution of subjects, study design (randomized, double-blind, parallel, crossover, etc.), the specific formulation and dosage size used, the control treatment(s), the dose range, and the duration of dosing. See Table 1 in Appendix A for an illustration of such a table.

   b. Reports of individual studies - order of presentation

      For each claim of effectiveness, studies should be grouped by study design (see 21 CFR 314.126 for definitions of the cited study designs), and within design, by other pertinent characteristics, as follows:

      1) Studies with a concurrent placebo control, including studies that include both placebo and active control

         a) Completed studies

            i. Domestic, with full case reports available
            ii. Foreign, with full case reports available
            iii. Published reports and other reports for which full case reports are not available.

         b) Ongoing studies with interim results

            i, ii, iii as above

         c) Incomplete studies no longer active

            i, ii, iii as above

A study should be considered incomplete only if it was terminated with very few patients. If it was stopped short of the projected population yet has a substantial number of patients, it should be analyzed as a complete study. If an applicant is undecided as to whether a particular study should be considered complete, and analyzed as such, the reviewing division should be consulted. When the sponsor considers a study incomplete, the basis for considering it incomplete should be provided.

2) Studies with dose-comparison concurrent control

   a), b), c) as above

3) Studies with a no-treatment concurrent control

   a), b), c) as above

4) Studies using an active concurrent control

   a), b), c) as above

5) Studies using explicit historical control that are considered by the sponsor to represent well-controlled studies, including those with a baseline observation period (patient as own control) and those using a distinct group of patients treated at another time, in another location, by another investigator, and/or in a separate study

   a), b), c) as above

Additional logical groupings within the above groups may be made by the sponsor, such as grouping by other study design feature (parallel, crossover, placebo withdrawal), by regimen (dose, dose interval), by duration, or by patient population (but if the population is so different that a separate claim results, the studies supporting each claim should be separated).

c. Reports of individual studies - content

For each study, there should be provided:

1) A brief synopsis, one to two pages in length, describing the study population, critical design features, and effectiveness and safety results, including critical numerical data.

A narrative description of the outcome without numerical data or a statement of the "statistical significance" of an effect is not useful. The use of tables is crucial to an efficient presentation.

2) The protocol (a plan for the study prepared prior to its conduct), including a sample of the case report form(s) used to carry out the study, and any protocol amendments made during the study. (The protocol should be placed as an appendix following the full report.) If several studies used an identical or nearly identical protocol, it need be included only once, with a reference to its location, and a description of any minor differences from the reference protocol appended to the report of each study.

3) Any publication that reports on or analyzes all, or any portion of, the data in the study. (The publication should be placed as an appendix following the report of each study.) If there are significant discrepancies between the data or analyses in the application and those in the published report, they should be explained.

4) A list of all investigators and other persons whose participation materially affected the conduct of the study and a brief description of their training (physician, psychologist, etc.) and of the role of each in the study, such as the particular observations or decisions for which each was responsible, should be provided as an appendix to the report. If there was an external (to the applicant) data monitoring group, its members should be included. A curriculum vitae or equivalent description of training and experience (e.g., biographical sketch format in PHS Form 398, Application for Public Health Service Grant) should be provided for each investigator as an appendix to the study report. This listing should include:

   a) Investigators

   b) Any person carrying out important study observations on a regular basis, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. Do not include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for a regular study participant.

c) The author(s) of the report, including the responsible statistician(s).

d) A statement [314.50(d)(5)(ix)] that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

5) A report of the study. Except as noted below, the description and analysis of the study should be the full report described in Section III of this guideline, for (a) all completed studies and (b) any ongoing studies with interim results that are intended to support effectiveness. Ordinarily, for completed studies or ongoing studies with interim analyses that on their face do not support effectiveness, for favorable studies that the sponsor considers flawed or unreliable, and for incomplete studies no longer active (see paragraph b.1).c) above), a briefer description of the results related to effectiveness (but sufficient to convey the outcome of the study quantitatively, even if no statistical analysis was performed) should be provided in addition to a brief summary of the study design and conduct. The reason for providing only the brief report should be given, if not apparent (e.g., the flaws that prevent the study from being relied upon). Any study with a statistically significant negative result (i.e., favoring placebo or other control therapy) or a strong negative trend should be reported in detail. For an ongoing study without interim analysis, of course, no effectiveness report is possible, and, except for serious adverse effects, there may also be little safety data available as well. Safety-related data should be presented thoroughly, as described below in Section III, for all these studies, even where a full analysis of effectiveness is not included. For any ongoing study subjected to either a full report or a briefer description and analysis, a projected completion date for the study should be given. For discontinued studies, the reason(s) for discontinuation should be given.

Non-supportive studies must not be simply ignored, even if their effectiveness results are not presented in complete detail. They should be discussed and analyzed in Section II G, Integrated Summary of Effectiveness Data. In addition, there should be exploration of the reasons for such "negative" or non-supportive studies, as they may suggest influences of study populations, dosages, study designs or other features that need to be understood. The brief description of these studies should provide information on these factors. Nonetheless, these studies in general will not benefit from the detailed description of study design and statistical methods, and analysis of effectiveness variables described in Section III.

The report should refer to the volume and page number where additional tabulations and case report forms for the study are located.

In some cases, particularly involving drugs that are being developed simultaneously in many countries, there will be a redundancy of controlled trials beyond what is reasonably needed to serve as a basis for evaluation of the drug, and preparation of the full reports described in Section III may be needlessly burdensome and unnecessary. It may also be difficult to obtain complete data when studies are conducted by a subsidiary of the U.S. applicant not familiar with the preparation of applications for submission to United States or European regulatory authorities. When such a situation is thought to exist, the applicant should initiate a discussion with the reviewing division to reach agreement on which controlled studies can be presented briefly, rather than in full report. Even the brief report, however, should provide a short description of the reported outcome of the trial regarding effectiveness and safety results and a complete evaluation and report of deaths, adverse dropouts, and other serious adverse events [see III.B.10.b.6)]. The report of the study should make clear the limitations of the analysis.

d. Overall summary of data from controlled studies

The applicant may provide an overall summary and evaluation of the data from controlled trials supporting each claimed indication, integrating the effectiveness and safety results of all trials. Preferably, however, this summary may be omitted and effectiveness data from controlled trials included only in the Integrated Summary of Effectiveness Data (Section II.G below). Similarly, the safety data from controlled trials should be included with other data in the section on Integrated Summary of Safety Information (Section II.H below).

E. Uncontrolled Clinical Studies [21 CFR 314.50(d)(5)(iii)]

1. Overview

Uncontrolled studies will not, in general, be useful in contributing to substantial evidence of the effectiveness of a drug, but they can provide support for the controlled studies and provide critical safety information for several reasons:

a. If the uncontrolled studies are relatively large compared to the controlled trials, uncontrolled studies may provide information on relatively rare events not likely to be seen in smaller studies.

b. In the absence of a control group it is difficult to determine whether adverse events common in the treated population even in the absence of drug exposure (e.g., those related to the underlying disease) are related to the test drug; uncontrolled studies can, however, identify uncommon events (liver injury, renal failure, hematologic events), events that reoccur on rechallenge, and events that bear a close temporal relationship to drug use and resolve on discontinuation of treatment.

c. The less strict entry criteria and control over concomitant treatment usual in such trials may sometimes allow identification of drug-drug or drug-disease interactions not evaluable in the controlled trials.

The section on uncontrolled studies should include all uncontrolled studies involving each claimed use of the drug, including incomplete or terminated studies, and studies from the clinical literature.

2. Format/content

The following information should be presented:

a. A table of all studies included in the section, grouped as described below. The table should list investigators, provide study identifiers (including protocol number and publication citation, if available), give the starting date of the study in the application, give the location of the full report of each study and its tabulations and case report forms, if any, and give the number, age range, and sex distribution of subjects, study design, the specific formulation and dosage size used, the dose range, and the duration of dosing. See Table 1 in Appendix A for an illustration of such a table.

b. Reports of individual studies - order of presentation

For each indication, studies should be grouped according to completeness and availability of case reports and within these groups by duration (shortest to longest), patient population, or other pertinent characteristics, as follows:

1) Completed Studies

    a) Full case reports available

        i. Domestic
        ii. Foreign

    b) Case reports not available, including published reports

2) Incomplete studies

    a) and b) as above

c. Reports of individual studies - content

For each study there should be provided:

1) A brief synopsis, one to two pages in length, describing the study population, study design, and important results. Safety-related data should be emphasized and tabular presentations used where appropriate.

2) The protocol, including a sample of the case report form(s) used to carry out the study, and any protocol amendments made during the study. (This should be placed as an appendix following the full report.) If several studies used an identical protocol it need be included only once, with a reference to its location appended to the report of each study.

3) Any publication that reports on or analyzes all, or any portion of, the data in the study. (The publication should be placed as an appendix following the report of each study.) If there are significant discrepancies between the data or analyses in the application and those in the published report, they should be explained.

4) A list of all investigators and other persons whose participation materially affected the conduct of the study and a brief description of their training (physician, psychologist, etc.) and of the role of each in the study, such as the particular observations or decisions for which each was responsible should be provided as an appendix to the report. A curriculum vitae or equivalent description of training and experience (e.g., biographical sketch format in PHS Form 398, Application for Public Health Service Grant) should be provided for each investigator. This listing should include:

   a) Investigators.

   b) Any person carrying out important study observations on a regular basis, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. Do not include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for a regular study participant.

   c) The author(s) of the report, including the responsible statistician(s).

   d) A statement [314.50(d)(5)(ix)] that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

5) A report of the study. For uncontrolled studies, the description of effectiveness results can be brief, generally omitting a statistical analysis entirely. It may be appropriate to expand the report if there is an important observation to be made or if the data are intended to support a claim or other section of labeling. If the uncontrolled study is an open extension of a controlled trial this should be noted and the results of the open study compared briefly with the controlled trial results. Except as noted below, analysis of safety-related information should be thorough, as described below in Section III. If it is not apparent why the study is considered uncontrolled (e.g., if the design seems to indicate a controlled trial), an explanation should be provided.

As was the case for controlled trials (see II.D.2.c.5), in some cases, particularly where a drug is being evaluated in many countries simultaneously, there may be a redundancy of information on the more common adverse events. With the agreement of the reviewing divisions, the less accessible studies may be reported more briefly. There should, however, be a complete evaluation and report of deaths, adverse dropouts, and other serious events for all uncontrolled studies [see III.B.10.b.6)]. The report of such studies should make clear the limitations of the analysis.

d. Overall summary of data from uncontrolled studies

The overall summary and evaluation of these studies should be incorporated into the integrated summaries of effectiveness and safety data (see Sections II.G and H below).

F. Other Studies and Information [21 CFR 314.50(d)(5)(iv)]

1. Overview

This section includes a description and analysis of any additional information obtained by the applicant from any source, foreign or domestic, that is relevant to the evaluation of the safety and effectiveness of the product. This information will, in general, be pertinent principally to the safety evaluation, as it includes results of controlled or uncontrolled clinical trials of uses of the drug other than those claimed in the application, commercial marketing experience, and reports in the literature or otherwise obtained, other than those cited in the Controlled Trials or Uncontrolled Trials sections above.

2. Format/content

The following information should be presented in this section:

a. A table of all studies and other information included in this section, grouped as described below. The table should, as applicable, list investigators, provide study identifiers (including protocol number and publication citation, if available), give the location in the application of the full report of each study and its tabulations and case report forms, if any, and give the number, age range, and sex distribution of subjects, study design, the specific formulation and dosage size used, the dose range, and the duration of dosing. See Table 1 in Appendix A for an illustration.

b. Reports of individual studies - order of presentation

Studies should be grouped according to design and availability of case reports, and within these groups by other pertinent characteristics in accordance with sponsor preferences, as follows:

1) Controlled studies of uses other than those claimed in the application, both complete and incomplete.

    a) Studies with case reports available.

    b) Published reports and other reports for which full case reports are not available.

2) Uncontrolled studies of uses other than those claimed in the application.

    a) Studies with case reports available.

    b) Published reports and other reports for which full case reports are not available.

3) Commercial marketing experience and foreign regulatory actions.

    a) List of countries in which drug has been approved, with dates of approval and a list of countries in which approval has been applied for with dates of application.

    b) All reports obtained from foreign regulatory authorities or foreign affiliates, licensors, or licensees of the applicant, including reports of, or analyses of, adverse effects, warning letters sent to physicians, and major changes in marketing status or labeling information resulting from marketing or other experience. A description should be provided of how information from each of these authorities and companies was sought.

    A copy should be provided of any letter from a foreign regulatory body that refuses drug approval on safety grounds. Copies of approved labeling from European countries, Canada, Australia, New Zealand, and Japan should be provided, with translation. Important differences from proposed U.S. labeling with respect to contraindications, warnings, precautions, adverse reactions, or dosing instructions should be identified and explained.

    - c) Epidemiologic studies.
    - d) Spontaneous reports from foreign marketing experience of serious adverse experiences [see 21 CFR 314.80(a)].
  - 4) Reports from literature or elsewhere not otherwise reported, with a description of the search strategy used to assess the world literature.
    - a) Published case reports, letters, etc.
    - b) Other information.

c. Reports of individual studies - groups 1), 2) - content:

  - 1) A brief synopsis, one to two pages in length, describing the study population, study design, and important results. Safety related data should be emphasized and tabular presentation used where appropriate.
  - 2) The protocol, including a sample of the case report form(s) used to carry out the study, and including any protocol amendments made during the conduct of the study. (This should be placed as an appendix following the full report.)
  - 3) Any publication that reports on, or analyzes all, or any portion of, the data in the study. (The publication should be placed as an appendix following the report of each study.) If there are significant discrepancies between the data or analyses in the application and those in the published report, they should be explained.
  - 4) A list of all investigators and other persons whose participation materially affected the conduct of the study and a brief description of their training (physician, psychologist, etc.) and of the role of each in the study, such as the particular observations or decisions for which each was responsible, should be provided as an apprendix to the report. A curriculum vitae or equivalent description of training and experience (e.g., biographical sketch format in PHS Form 398, Application for Public Health Service Grant) for each investigator should be provided as an appendix to the study report. This listing should include:
    - a) Investigators.

b) Any person carrying out important study observations on a regular basis, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. Do not include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for a regular study participant.

c) The author(s) of the report, including the responsible biostatistician(s).

d) A statement [314.50(d)(5)(ix)] that the study was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under section 56.104 or section 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

5) A report of the study. The description and analysis of effectiveness results can be brief, generally omitting a statistical analysis entirely, although it may be expanded if the applicant has reason to do so. Analysis of safety-related information should be thorough, as described in Section H below, except in cases where, with the agreement of the reviewing division, a more limited analysis is considered acceptable [see II.D.2.c.5) and II.E.2.c.5)].

d. For commercial marketing experience (group 3) reports should explain the nature of the reported observations, the reporting system, the number of patients who received the drug or amount of drug distributed, etc., as appropriate.

e. Overall summary of other studies and information

The overall summary and evaluation of these studies and other information should be incorporated into the integrated summaries of effectiveness and safety data (see Sections G. and H. below).

G. Integrated Summary of Effectiveness Data [21 CFR 314.50(d)(5)(v)]

The content of this section should be included in both the clinical and statistical technical sections.

1. Overview

This section should provide an integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication. It should also include a summary of evidence supporting the dosage and administration section of the labeling, including the dosage and dose interval recommended, and evidence pertinent to individualization of dosing and need for modifications of dosing for specific subgroups (e.g., pediatric or geriatric patients, or patients with renal failure). If certain subgroups that are candidates for treatment with the drug have not been included (e.g., older patients), so that the effectiveness of the drug has not been assessed in them, this should be noted and the implications considered.

The individual controlled studies to a great extent speak for themselves with respect to their ability to provide the evidence of effectiveness required by law. This section should provide an overview of the results, showing that they do satisfy the regulatory requirements for approval, i.e., represent adequate and well-controlled studies demonstrating the claimed effect, particularly if results are inconsistent or marginal. For example, the sponsor would explain here his basis for seeking to rely on a single study. Equally important, this section should include an examination of study-to-study differences in results, effects in subsets of the treated population, dose-response information from all sources, any available comparisons with alternative drugs, and any other information, so that the nature of the drug's effectiveness can be as fully defined as possible, and the user of the drug can be given the best possible information on how to use the drug and what results to expect.

2. Format/Content

Format for this section cannot be rigidly described. The applicant should take note of the suggestions for content below but should choose the format that best suits the data.

a. Identification of studies fulfilling the statutory requirements for adequate and well-controlled studies showing that the drug has its intended effect.

If the intended or claimed effect is on a "surrogate" endpoint, i.e., not the ultimate reason for treatment, e.g., to reduce mortality or morbidity, but an endpoint more readily measured and thought to be related to, and likely to predict, a favorable effect on the ultimate endpoint, the basis for choice of the endpoint should be discussed and its validity supported. In some cases, established Agency policy may decrease the need for this discussion and it may be sufficient to refer to past Agency decisions (e.g., antihypertensive, oral hypoglycemic, and lipid-lowering agents have generally been approved on the basis of demonstrated effects on blood pressure, blood sugar, and blood lipids, respectively without evidence, at the time of approval, of an effect of the particular drug on survival or morbidity.)

b. Comparison and analysis of results of all controlled trials

The objective of this section is to define the effect of the drug in the studies that were carried out.

Generally with the help of tables showing major study design features, numbers of patients, number of dropouts, and major outcomes, and consistent with the report of individual study results described above, the results from all controlled trials, including those well-controlled studies that did not favor the study treatment and including controlled trials (e.g., single dose studies) that were included under clinical pharmacology, should be summarized, examined, and compared. In comparing study results, if many variables or time points were analyzed, representative ones, usually those that were identified as the primary endpoints in the individual studies, should be selected for display and evaluation. Ordinarily, studies with similar controls (placebo control, active control) should be discussed together. A variety of methods have been used to compare study results, including study-by-study display of results (and confidence intervals) such as mean differences from placebo (illustrated by Figure 1 in Appendix A), relative risk, or odds ratio [see Figures 1, 2, page 185 in Yusuf et al: Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. European Heart J. (1985) 6, 556-585] or "scattergrams" showing treatment on one axis and placebo on the other, the 45° line representing a no-effect line.

It is generally not helpful to pool results from individual studies not designed for analysis in that fashion, but if the applicant wishes to offer such an analysis, it should be presented in full in this section. If such pooling is attempted, particular attention should be paid to statistical considerations, selection bias in choosing studies, etc.

If there are important differences in outcome between studies of generally similar design, an attempt (admittedly often difficult) should be made to explain why results were different. Factors such as differences in patients (disease definition, disease stage, severity, prior treatment), in drug dose or regimen, in methods of observation, in adherence to protocol, or inadequate power (high beta error rate) may offer such an explanation and should be considered and any important differences displayed. Often such analyses will raise questions for future exploration rather than provide definitive answers.

c. Results of uncontrolled studies

Uncontrolled studies should be discussed to the extent they contribute supportive evidence of effectiveness. If controlled trials are plentiful and strongly supportive, it should not be necessary to provide more than a tabular display of the results of the uncontrolled studies.

d. Analysis of dose-response or blood level-response information

There should be an integrated summary and analysis of all data, from animal, pharmacokinetic, pharmacodynamic and other clinical pharmacology studies, and from controlled and uncontrolled clinical studies, that bear on the dose-response or blood level-response relationship of effectiveness, the dose-blood level relationship, the method of dose selection, and the choice of dose-interval, and that support the dosing recommendations proposed in labeling, including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualization of dosage. Any identified deviations from relatively simple dose-response or blood-level response relationships due to non-linearity of pharmacokinetics, delayed effects, tolerance, enzyme induction, etc. should be described and their implications for clinical usage discussed. Limitations of the data, e.g., because the study design did not permit evaluation of effects at each dose, should be candidly exposed and any plans for further studies disclosed. If dosing recommendations are different from those in other countries, the differences should be explained. The analysis of effectiveness dose-response can be separated from and referred to in, or integrated with, a similar section of the Integrated Summary of Safety Data.

Any evidence of different dose-response relationships in age, size, sex, disease, or other subpopulations should be described, including evidence of different pharmacokinetic or pharmacodynamic responses. The ways in which such differences were looked for, even if none were found, should be described (e.g., specific studies in subpopulations, analysis of effectiveness results by subgroup, or blood level determinations of test drug).

e. Analysis of responses in subsets of the overall population: drug-demographic, drug-drug, and drug-disease interactions

Although analysis of responses in subsets of the population, particularly when they are devised and carried out after the study is complete, cannot carry the same statistical or clinical weight as a study designed to test a prior hypothesis, available data should be examined for consistent differences in response among reasonable subsets of the overall population, at least with respect to the effectiveness seen in trials, to the dose needed, and to pharmacokinetic responses (as assessed by blood level measurements during clinical trials or by formal pharmacokinetic studies). Subsets of interest will vary with the drug and condition studied but would usually include: sex, race, age, and size, and might include disease severity, concomitant illness, concomitant drug, smoking and ethanol usage history, and prior therapy. The numbers of exposed patients in the major subsets (age, sex, race) should be displayed or referred to if such a tabulation appears in the Integrated Summary of Safety Information. The examination of subsets need not routinely involve formal statistical analysis. Of interest are differences of clinically meaningful size. If these are not observed, minor differences, likely to reflect the fact that multiple subsets have been analyzed rather than true differences, should be described, but need not be analyzed further.

f. Evidence of long-term effectiveness, tolerance, and withdrawal effects

Drugs for chronic use are not usually studied for the full intended period of use, but are generally studied for periods of 6 months to a year. Available information on persistence of effectiveness over time should be summarized and evidence of tolerance or withdrawal effects noted.

H. Integrated Summary of Safety Information [21 CFR 314.50(d)(5)(vi)]

The content of this section should be included in both the clinical and statistical technical sections.

1. Overview

This section should integrate safety information from all sources, including pertinent animal data, clinical pharmacology studies, controlled and uncontrolled clinical trials (including controlled trials for indications not claimed in the application), and foreign marketing experience or epidemiologic studies related to any use of the drug. Dose-response and blood level-response relationships for adverse effects should be identified, as should drug-drug or drug-disease interactions, and any demographic or clinical features that predispose to adverse effects, such as age, renal or hepatic impairment, etc. A description of any statistical analyses not included under the individual study report should be provided.

While other parts of the application present safety results of each study, the integrated summary is an overall analysis, examining all studies together. This allows examination of differences among population subsets not possible with the relatively small numbers of patients in individual studies and, especially important, allows evaluation of more serious adverse effects too rare to be detected with assurance in single studies. Thus, the integrated summary is, in part, simply a summation of data from individual studies and, in part, a new analysis that goes beyond what can be done with individual studies.

In every analysis and display it is critical that the data base used (all studies, certain studies, certain patients in certain studies such as those exposed for a particular period, etc.) and the numbers of patients involved in the analysis (the denominator) be given. The denominator is critically important and must be chosen with care. In calculating adverse event rates not all exposed patients are at risk of certain events; e.g., most drug-related liver injury requires exposure of several weeks, so that short-term studies should probably not be part of the denominator for rate of liver injury. The rates should be based on the relevant exposed population.

If the relevant population is uncertain, more than one denominator (all patients, all patients exposed for one month or more, etc.) can be used.

If a potentially important adverse reaction is expected (e.g., because of an animal finding or because it is thought to be an effect associated with the pharmacologic class) but is not seen, or is seen no more often than in a placebo group, it is important to discuss how the effect was sought and the ability of the studies to have found such an effect had one been present.

Updates of safety information are required under the regulations to include "new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling," in essentially the same format as the integrated summary. Because the content of the update will depend on the nature of the additional data, it will generally be useful to consult with the reviewing division before preparing the update. It is possible to provide the safety update information as a report that refers only to the new data obtained since the last update or since the original submission, but it is preferable to provide a document incorporating the new data with the data and analyses in the initial integrated summary of safety information, as well as showing the new data. If the additional data are relatively few and come principally from foreign sources or other studies that have not been incorporated into overall analyses in the initial submission, it may be sufficient to concentrate on the serious or potentially serious adverse events, or an unusually high frequency of a less serious event, providing a narrative description of these events. The regulations require that case report forms be provided for all patients who died in a clinical study or, unless the requirement is waived, who failed to complete a study because of an adverse experience.

2. Format/content

   a. A table of all investigations pertinent to safety, identified by protocol number and principal investigator, grouped by type (clinical pharmacology, adequate and well-controlled studies, uncontrolled studies, and other studies), and including studies of indications other than those sought in the application giving:

      1) Type of study (controlled, double blind, randomized, etc.)
      2) Status (continuing, discontinued)
      3) Location of full report
      4) CRF's, available or not
      5) Number of patients on each treatment
      6) Indication studied
      7) Age range of patients in each study and sex/race distribution
      8) Duration of drug exposure in the study
      9) Dose range in the study
      10) Frequency of dosing

      (The tables prepared for earlier sections, II.C-F, may be reproduced here.)

   b. Overall extent of exposure

      The extent of exposure to active drugs (number of patients exposed in all studies, duration of exposure, and dose) should be described in tables, including:

1) Number of patients exposed altogether and for specified periods of time, e.g., one day or less, more than one day to one week, more than one week to one month or more than one month.

   The numbers should be given for sex and for other particularly relevant demographic subgroups, such as the geriatric age group. A life-table presentation may be an efficient way of displaying duration of exposure. Patients included in more than one study (e.g., a controlled trial followed by a long-term extension) should be counted only once. If it cannot be determined whether the same patient appears in more than one study, this should be indicated. If certain subgroups that are candidates for treatment with the drug have not been included (e.g., older patients), so that the safety of the drug has not been assessed in them, this should be noted and the implications discussed.

2) Number of patients exposed to various doses for defined periods.

   This can be difficult to display. One simple way to do this is to attribute to each patient the dose he was on for the longest time, providing a crude, but reasonable, picture of exposure. This, however, underestimates the total exposure to a particular dose. Alternatively, it is possible to count each dose duration segment for each patient exposed to several doses. Thus, a patient given 3 different doses for 3 different months would be counted 3 times, as an exposure at each of 3 doses. It may simplify the display to group a range of doses as low, medium, and high. There are no doubt many other reasonable ways to display exposure; the applicant should consult with the reviewing division if in doubt.

c. Demographic and other characteristics of study population

The relevant demographic, baseline, and other characteristics of the study population will depend on the drug, but will usually include:

1) Age, both mean and numbers within defined ranges, such as decades
2) Sex
3) Race
4) Body weight
5) Primary diagnosis
6) Secondary diagnoses
7) Concomitant therapy taken during the study
8) Smoking status and history
9) Ethanol use

10) Relevant prognostic variables (e.g., the frequency of such adverse events as arrhythmias, sudden death, or heart failure is affected by such prognostic factors as previous acute myocardial infarction)

These should be presented for the entire drug-exposed population and for logical groups of studies, such as all controlled trials, short-term trials, longer term trials, etc., preferably the same groupings used in displaying adverse experiences (see next section).

The groups should be defined clearly and the studies included specified. For the controlled trials, a similar display should be provided for control agents.

d. Adverse experiences in clinical trials

1) The overall adverse event experience in all studies should be described in a brief narrative, supported by the following more detailed tabulations and analyses.

2) Display of adverse events and occurrence rates

All new adverse events (i.e., those not seen at baseline or that worsened during treatment), which are sometimes called treatment emergent signs and symptoms (TESS), should be summarized in tables listing each event, the number of patients in whom the event occurred, and the rate of occurrence in treated patients (patients exposed in more than one trial should be counted in a denominator only once).

a) Grouping of studies

The rate for all studies pooled (i.e., the number of patients with an event divided by all exposed patients), but excluding short-term studies, may be calculated, but it is usually not the best measure of true event rates; grouping studies in some fashion, however, can often give a better estimate of the usual response than analysis of single studies can.

Ordinarily, separate analyses should be made of studies with available case report forms and those studies that lack them. Any studies not subjected to a full safety analysis, per agreement with the reviewing division [see II.D.2.c.5), II.E.2.c.5), and II.F.2.c.5)], should not be included in the denominators of the adverse event rates for which they were not analyzed in full.

Among the studies with CRF's, various groupings should be considered, including:

i. All controlled trials, or subsets of controlled trials, such as all placebo-controlled trials, trials with any positive control, trials with a particular positive control, or trials of particular indications (and thus carried out in different populations)

These studies are the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. For such trials, of course, rates in control and treatment groups should be compared.

ii. All trials, excluding short-term studies in normals

Short-term studies in patients also would usually be excluded and presented separately. Note, however, that this analysis should not exclude patients in longer studies who left the study early because of intolerance; only planned short-term studies would be omitted.

iii. All trials of roughly similar duration

iv. Trials in which adverse event reports are elicited by checklist or direct questioning and those in which events are volunteered

v. Foreign trials; domestic trials

It is almost always useful to carry out the groupings suggested in i and ii; the others chosen will vary from drug to drug and will be influenced by inspection of individual study results. Whatever methods are used, it must be recognized that, as for single trial results, any specific numerical rate is a rough approximation at best, and represents a result in a specific population, with specific observers, and with specific observation techniques. The range of adverse event rates in various studies may thus be as important as any arbitrarily constructed mean.

b) Grouping of events

Adverse events should be grouped by body system, as shown in the individual study report (see Section III.B.10.b.). In combining data from many different studies it is important to use standardized terms to describe events and collect synonymous terms under a single primary term. This can be done with a standard dictionary (e.g., COSTART, which is used to classify post-marketing terms) or another method. Rates should be presented for primary terms (defined or referenced to a dictionary) or as a single value for a defined group of terms (e.g., heartburn, indigestion, or dyspepsia might be considered a single adverse event).

The primary terms should be grouped by body system and arranged in decreasing frequency, and should be divided into severity categories. They may be further divided into those considered related to drug use and those not considered so related, with an explanation of how such determinations were made.

3) Analysis of adverse event rates

Once rates of adverse events are calculated for the various study groupings, they can be analyzed in various ways. For controlled trials, rates should be compared in treatment and control groups and events that appear unrelated to treatment should be identified (e.g., those that appear at approximately equal rates and severity in both groups in a placebo-controlled study state). In these comparisons, as in any analysis of controlled trials, attention should be paid to comparability of groups for pertinent variables.

In uncontrolled studies, comparisons with a concurrent control are not possible; it may be useful to compare treatment with baseline periods and to compare rates in controlled and uncontrolled studies, especially where patient populations are similar.

The more common adverse events, especially if serious or very troublesome to patients, that appear to be related to drug use should be analyzed for relationship to dosage, to mg/kg dose, if weight data are available, to dose-interval, to duration of treatment, to cumulative dose or dose-exposure time product in some cases, to demographic characteristics such as age, or to other baseline features, such as renal function, and to blood level, if blood level data are available. As in the case of similar analyses of effectiveness, minor differences should be described but need not be analyzed with rigorous statistical methods. It is substantial differences, potentially useful to the prescribing physician, that are sought in such analyses. If a finding of "no difference," e.g., no evidence of an increasing rate of an important adverse event with age, is considered important or a potential labeling claim, there should be an analysis of the statistical power or confidence limits of the finding.

A final display of adverse reaction rates should be developed for use in labeling. Many ways of displaying the data in labeling have been utilized and discussions with the reviewing division will be useful.

4) Display and analysis of deaths, dropouts due to adverse events (adverse dropouts), and other serious or potentially serious adverse events

The lists of patients who died or who left a study prematurely due to adverse events, and patients with other serious or potentially serious adverse events from individual studies should be combined for this section to make overall lists of deaths, adverse dropouts, including laboratory abnormalities leading to termination, and other serious adverse events. As in the individual studies, the listing should include a patient identifier and the information called for in Section III.B.10.b.5), the study identifier, the location of the report, and the location of the narrative description of the event. Alternatively, it may be convenient to reproduce these narrative descriptions in this section. For these overall lists, the adverse events should be grouped by body system and within systems by reactions of the same general type.

In addition to the individual patient listings, if there are many deaths and adverse dropouts, it will be helpful to give rates of such events in a table similar to that for all adverse reactions (see Table 2 in Appendix A for an example of such a table for controlled trials; a similar table could be made for uncontrolled studies or for all patients in trials of more than a certain duration, such as one day).

The significance of these serious and potentially serious adverse events should then be evaluated from at least two points of view.

a) The recognized and clearly drug-related events that lead to dropping out or death, even if they are expected effects of the drug, represent the most important safety concerns associated with use of the drug, as indicated by the outcome and investigator behavior. They deserve particular attention in labeling with respect to warning information and to specification of any steps that can be taken to avoid, mitigate, or treat them. In addition, the data base should be searched for any feature that seems to increase the risk of these events, such as a patient demographic characteristic (age, sex, race), a concomitant illness (such as renal failure), dosage above a certain level, or particular concomitant treatment.

b) The serious, potentially life-threatening events that are not known to be drug-related should be searched for clues to an unexpected drug relationship. It has historically been tempting to consider as intercurrent illness, or as related to the underlying disease, adverse events that in retrospect were drug-related. It should be appreciated that in most treatment populations of 1000-2000, screened at baseline for major abnormalities and basically well except for a specific illness, such events as acute hepatitis, acute renal failure, aplastic anemia, agranulocytosis, thrombocytopenia, seizures, ventricular tachyarrhythmias, gastrointestinal hemorrhage, stroke, pulmonary embolism, acute myocardial infarction, peripheral arterial obstruction, or sudden death are unusual and will usually not occur in the course of a several-month period of observation. Any such events deserve close scrutiny, comparison between treatment groups, and, if possible, comparison with historical series of the same patients.

Obviously, certain populations will be pre-disposed to some of these kinds of events, but the extent of such predisposition should be evaluated with available data, not assumed.

It may not, indeed often will not, be possible to decide whether a particular serious event is drug-induced, but such events should be noted for future review and consideration in the post-marketing period and perhaps identified in labeling as a possible adverse effect of uncertain relationship to the drug. Steps planned to evaluate adverse events further should be noted.

Either of the above analyses may be facilitated by use of life table approaches (or cumulative occurrence tables) to define risk in relation to time on drug. This may be done by grouping all patients from all studies (see Appendix A, Table 3) or by examining studies individually (see Appendix A, Table 4).

e. Clinical laboratory evaluation in clinical trials

This section should combine data from individual studies, using analyses similar to those in individual study reports, such as changes in mean or median, analysis of shifts in individuals, and analysis of individual marked abnormalities, to provide an overall analysis. The number of patients included in any analysis (number who had a particular test) should be clear. It will generally be appropriate to include separate analyses of studies that include a control, where the control can assist in the interpretation of changes seen, and those that do not, where the only comparison available is with the patient's own baseline.

Any clinically significant abnormality found in one or more patients should be discussed, unless it has been considered earlier under adverse dropouts, and it is usually useful to examine smaller deviations of the same parameter in other patients, and closely related measurements.

It may be useful to display relationships between laboratory tests (e.g., to identify the numbers of patients with both elevated transaminase and elevated bilirubin), to look at clinically relevant subsets of patients (e.g., those with a specified abnormality on more than one measurement), or to examine relationships between particular adverse events and particular laboratory abnormalities. The patients identified as having both events (both lab abnormalities or the ADR and the abnormality) or being in the clinically relevant subset of lab abnormalities can then be examined more closely.

As for the analysis of adverse events, relationship of drug-related abnormalities to dose, to mg/kg dose to duration of treatment, to cumulative dose, or to particular patient characteristics (age, renal or hepatic function abnormalities, concomitant illness, etc.) should be explored. The particular results seen with any drug will often suggest further analyses.

The fact that different laboratories utilize different normal values can pose a problem. However, data based on the same test method may be grouped. The method for doing this should be described. It may be necessary to "normalize" some lab parameters, such as transaminases, so they can be combined across studies (i.e., record percent above upper limit of normal rather than actual value).

f. Adverse events, including laboratory abnormalities, from sources other than clinical trials

All sources of adverse events, other than trials, including foreign marketing experience (information from regulatory authorities, foreign subsidiaries, journal articles, letters to the editor), formal epidemiologic studies, etc., should be summarized. The procedures used to examine these sources, including the method used to search the world literature, should be described.

g. Animal data

Animal data pertinent to human safety should be summarized (reference to the overall summary may be sufficient), particularly including results of carcinogenicity testing and reproductive testing. The implications of comparative ADME studies should be discussed. Planned additional studies or repetitions of studies should be described and the implications of any important findings for labeling, use restrictions, etc., discussed.

h. Analysis of adverse effect dose-response information

There should be an integrated analysis of all data, from animal, clinical pharmacology, controlled and uncontrolled studies, that bear on the dose-response and blood level-response relationships of adverse effects, the method of dose selection, and the choice of dose-interval, and that support the dosing recommendations proposed. Particular attention should be paid to the comparison of effectiveness and adverse effect dose-responses (the "therapeutic ratio"). The implications of this analysis for individualization of therapy to minimize adverse effects while maintaining effectiveness should be discussed.

Any evidence of different dose-response relationships in age, sex, disease, or other subpopulations should be described. The ways in which such differences were looked for, even if none were found, should be described (e.g., specific studies in age or sex subpopulations, or in patients with renal or hepatic impairment or specific concomitant illness; analyses of adverse event rates by subgroup; use of trough and/or other blood level determinations of drug, etc.).

i. Drug-drug interactions

Formal study of all possible interactions is impossible, but the application should include a frank discussion of available data:

1) Potential interactions

Theoretically likely interactions, such as those predictable from the known pharmacologic properties of the drug (e.g., effects on protein binding, on renal or hepatic blood flow, or on hepatic enzymes, or interactions known to occur with other members of the pharmacologic class) should be identified.

2) Drugs likely to be co-administered with the new drug in clinical use should be identified.

3) All data bearing on drug-drug interactions should be summarized, including:

a) Formal pharmacokinetic and pharmacodynamic studies

b) Experience from clinical trials

The concomitant therapies used in all studies should be listed and the number of patients using each concomitant drug while exposed to the test drug given. These concomitant therapy subgroups should be examined for any unusual adverse event profile. Such an evaluation is not nearly so rigorous as a formal trial intended to study potential interactions but as it is impossible to study all potential interactions, this analysis provides some assurance that major effects are not present.

It may also be useful to examine trough or other blood levels of critical concomitant therapy (e.g., digoxin, theophylline, antiarrhythmics) before and during use of the test drug, looking for changes in relation to test drug use (a "drug interaction screen").

j. Drug-demographic and drug-disease interactions

Data bearing on drug-demographic and drug-disease interactions should be summarized, including:

1) Formal pharmacokinetic and pharmacodynamic studies

2) Experience from clinical trials should be analyzed as for drug-drug interactions, above, with emphasis on diseases or demographic features that could alter metabolism or distribution of drug, to look for features that are associated with more frequent or more severe adverse effects.

k. Pharmacologic properties other than the property of principal interest

For almost any drug in any pharmacologic class, it is important to have a reasonably complete pharmacologic profile. We know, for example, that CNS drugs can have profound cardiac effects, and cardiac drugs profound CNS effects. Certain kinds of data seem relevant to almost any drug and the availability of such information is relevant to any reviewer.

The application therefore should describe the available data from human and animal studies about other pharmacologic properties of the drug, especially those that have proved often to be pertinent to the use of drugs, particularly to their unwanted effects and drug-drug interactions, including:

- effects on liver blood flow or liver metabolizing enzymes,
- effects on renal blood flow, GFR, or renal concentrating mechanisms,
- effects on the electrophysiologic properties of the heart,
- effects on hemodynamic measurements,
- effects on the sympathetic or parasympathetic nervous systems,
- effects on CNS function,
- effects on endocrine function, and
- effects on immunologic functions

Evaluation of these properties does not necessarily require formal human pharmacologic study. It might, for example, be reasonable to conclude from controlled trials that show no sedation or dry mouth that a drug does not have sedative or anticholinergic properties. Sometimes results of clinical trials will suggest more formal study; any planned further study should be described.

l. Long-term adverse effects

Available long-term (6 months or more) data should be summarized and delayed adverse effects identified.

m. Withdrawal effects

Specific studies of withdrawal effects and evidence from withdrawal events that occurred in the course of clinical trials should be summarized.

3. Update of Safety Information [21 CFR 314.50(d)(5)(vi)(b)]

(As noted above, not all of the following sections may be necessary, especially if additional data are few, or represent principally marketing and other open experience, and would not alter the data and conclusions in the original integrated summary of safety information materially.)

a. Table of new investigations (or added data in previously reported investigations), as in Section II.H.2.a above.

b. Additional extent of exposure and, if total exposure has been substantially changed (as a rule of thumb, increased by 25% or more), reanalysis of total exposure as in Section II.H.2.b above.

c. Demographics of additional exposure and reanalysis of total exposure as in Section II.H.2.c, if exposure has substantially changed.

d. Adverse experiences in new investigations, analyzed and displayed as in Section II.H.2.d above. If the new exposure is substantial, i.e., a 25% increase or more, an overall analysis examining both the new and old data together should ordinarily be carried out, using the same displays and analyses as in the original submission, as described in Section II.H.2.d. If the new data overall lead to conclusions that are substantially different from conclusions based on earlier data, it will be necessary to examine possible causes of the differences, and it may be necessary to provide complete reports of the safety aspects of individual studies, as described in Section III.

As indicated earlier, the reviewing division may decide that some of these analyses will not be useful; e.g., if the data base is already very large, further analysis of the more common adverse events may not be helpful. In that event, detailed analysis might be restricted to deaths, adverse dropouts, and other serious or potentially serious adverse events (see Section II.H.2.d.4) above), to less serious events of particular interest based on the analysis in the initial submission, and to events in particular subpopulations not well represented in the initial submission (e.g., elderly patients or patients with impaired renal or hepatic function).

e. Clinical laboratory evaluation

New data should be presented as described above for adverse experiences in the new investigations (II.H.3.d).

f. Adverse events from sources other than clinical trials

New data in these categories, including an update of the search of the world literature, should be provided as described in Sections II.H.2.f, II.F.2.b.3) and 4), and II.F.2.d.

g. Other analyses

Ordinarily, it will not be necessary to provide the additional analyses of dose-response, drug-drug interaction, or drug-demographic or drug-disease interaction (Sections II.H.2.h-j) unless the new data are very extensive and substantially improve the ability to carry out such analyses. Relevant animal data and information on other pharmacologic properties, long-term adverse effects, or withdrawal effects should be provided (see Sections II.H.2.g and II.H.2.k-m).

I. Drug Abuse and Overdosage Information [21 CFR 314.50(d)(5)(vii)]

If a drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act, should be provided. If the drug is pharmacologically or structurally related to another drug known to have abuse potential, and studies of its abuse potential have not been performed, the reasons these studies are considered unnecessary should be discussed.

Studies related to overdosage and any observed instances of overdosage should also be provided, including information on dialyzability, antidotes, or other treatments. Animal data may be useful.

J. Integrated Summary of Benefits and Risks of the Drug [21 CFR 314.50(d)(5)(viii)]

Ordinarily the integrated summary of benefits and risks can be a brief recapitulation of the main evidence of effectiveness and the main adverse effects, showing that under the conditions of use defined in labeling, the expected benefits of use exceed the risks. In some cases, however, more detailed discussion is needed to deal with difficult risk/benefit decisions. When to provide such discussion must be left to the applicant, but the following situations suggest a need for special attention:

1. Presence of a particularly severe known or potential human toxicity (such as hepatotoxicity, induction of seizures, severe hematologic toxicity, induction of severe birth defects, abortifacient properties), especially if frequent. In that case, use of the drug may need to be directed, through labeling or other means, to particular subsets of patients, and special precautions may be needed. It will generally be necessary to consider the risks and benefits of alternative therapies and to consider a possible role for the new drug only as a "not for initial use" or as a "last resort" agent.

2. A positive or possibly positive carcinogenicity finding requires detailed discussion, including whether or not use of the drug needs to be limited because of it and whether there is need for repeat studies.

3. Marginal effectiveness or inconsistent evidence of effectiveness bears discussion, especially in relation to other drugs for the same purpose. The poor results could, among other reasons, reflect poor study design in some of the studies, lack of available patients for study due to the presence of effective marketed drugs, or a truly marginal effect.

4. A particularly limited data base, often all that is obtainable for drugs intended for relatively rare diseases, calls for some discussion, e.g., of plans to obtain additional data after marketing or why the data base should be considered sufficient.

5. When the claimed effect is on a "surrogate" endpoint, i.e., not the ultimate reason for treatment, such as to reduce mortality or morbidity, but on an endpoint more readily measured, and thought to be related to, and likely to predict, a favorable effect on the true endpoint, discussion of the risks and benefits of the drug should reflect this. (Note also need for discussion in Integrated Summary of Effectiveness data, G.2.a.)

The applicant should address in this section any important risk/benefit questions that remain unanswered, particularly potential safety problems whose evaluation awaits further data, and should detail plans for further study or evaluation to resolve the unanswered questions.

III. THE FORMAT AND CONTENT OF THE FULL INTEGRATED CLINICAL AND STATISTICAL REPORT OF A CONTROLLED CLINICAL STUDY

A. Introduction

The study report described in this section is an "integrated" full report in which the clinical and statistical descriptions, presentations, and analyses are integrated into a single report, incorporating tables and figures into the main text of the report, or at the end of the text, and with appendices containing the protocol, investigator information, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output, etc. The integrated full report should not be derived by simply attaching a separate statistical report to the clinical report. The format and content of the full integrated report of a controlled clinical study described in this section is based on previous separate clinical and statistical draft guidelines and describes a report that will satisfy the needs of both disciplines. Specific statistical issues, including discussions of dropouts and missing data, multiple investigator studies, interim analysis, adjustments for covariates, multiple endpoints, use of an "efficacy subset," and active control studies, now appear in Section III.B.9.c.2). A discussion of machine-readable data bases is presented under Section III.B.9.d.2). and Appendix B. Finally, the discussion on protocol and protocol cover sheet now appears in Appendix C.

The following description of the data that should be provided in a complete description and analysis of a study reflects what is needed for a controlled clinical trial in which there is equal interest in both the effectiveness and safety information. For uncontrolled studies or studies of conditions for which no claim is made in the application (Sections II.E and F above), or controlled studies that plainly do not show effectiveness or that are flawed in design or conducted such that they should not be considered as contributing to evidence of effectiveness [see Section II.D.2.c.5)], the effectiveness results and details of design (Sections III.B.6-9) may be presented more briefly. Safety aspects of these studies, however, should be treated as described in this section.

Clinical pharmacology studies vary greatly in design and need for detailed analysis, but, in general, the detailed presentations should be similar to those for a well-controlled study, adapted as appropriate to the specific situation.

The guidance provided below is more detailed than guidance provided in the past and is intended to notify the applicant of virtually all of the information that need routinely be provided so that post-submission requests for further data and analyses can be reduced as much as possible. Nonetheless, specific requirements for data presentation and analysis, especially related to demonstration of effectiveness, vary from drug class to drug class and cannot be described in general terms; it is therefore important to refer to specific clinical guidelines and to discuss data presentation and analyses with the reviewing division.

The report should provide enough information on the methods and conduct of the study so that there is no ambiguity in how the study was carried out and should provide enough individual data, including the demographic and baseline data used to assess group comparability, and details of analytic methods, to allow replication of the critical analyses. It is also particularly important that all analyses, tables, and figures carry, in text or as part of the table, clear identification of the patient population base from which they were generated.

Analysis of safety-related data can be considered at three levels. First, the amount of exposure (dose, duration) should be examined to determine the extent to which safety can be assessed from the study. Second, the more common adverse events, including laboratory test changes, should be identified, classified in some reasonable way, compared for treatment groups, and analyzed, as appropriate, for factors that may affect the frequency of adverse reactions, such as time dependence, relation to demographic characteristics, relation to dose, cumulative dose or blood level, etc. Finally, potentially serious, but less common, adverse events should be identified, usually by close examination of patients who left the study prematurely because of an adverse event or who died.

The full integrated report of the individual study will include the most detailed discussion of individual adverse events or laboratory abnormalities, but it is usually essential to reexamine these as part of an overall safety analysis of all available data (Section II.H).

In presenting the detailed description of how the study was carried out, it may be possible simply to restate the description in the initial protocol. Often, however, it is possible to present the methodology of the study more concisely in a separate document. In each section describing the design and conduct of the study (Sections II.B.6-9), it is particularly important to clarify features of the study that are not well-described in the protocol and identify ways in which the study as conducted differed from the protocol.

At several points, detailed patient data listings are requested (demographic and baseline data, effectiveness data, certain safety data). The full data extracted from case report forms are provided in the case report tabulations (Section IV), but these, being entirely comprehensive, serve as an archival or reference document, not as listings suitable for ordinary review. The data listings requested as part of the report (in an appendix to it) are focused on the particular variables critical to the analyses carried out, allowing the reviewer to examine the individual patient data underlying critical group measurements. While in general it is desirable to include as many variables as possible in a single listing, this should not be at the expense of clarity. An excess of data should not be allowed to lead to overuse of symbols instead of words or easily understood abbreviations, too small displays, etc. It is preferable to divide the tables.

In any data listing, imputed values, if used, should be identified in a conspicuous fashion. Detailed explanations should be provided as to how such imputations were done and what underlying assumptions were made. Imputations should, however, be avoided as much as possible, as they are potentially biased and likely to lead to disagreement or controversy.

In general, a study planned as a multicenter study, in which all centers are analyzed, can be presented as a single study with the investigator as a covariate or blocking factor. Any critical differences between clinics in the conduct of the study should be noted and the impact of such differences assessed. Key efficacy measures should be displayed by investigator and the larger studies should be analyzed separately. See Section III.B.9.c.2)d) for additional comments on multicenter studies.

It cannot be emphasized too strongly that in the following outline the specific sequence is not critical, but the topics listed should be considered and omitted only if clearly not pertinent. Additional topics might be added at appropriate places if necessary.

B. The Full Integrated Clinical and Statistical Report of a Controlled Clinical Study

The report of an individual study should generally include the following:

1. Title page

The title page should contain the protocol number (or other identifier), the title of the report, the name and affiliation of the investigator(s), the names and telephone numbers of the sponsor's staff members who should be contacted for clinical and statistical questions, the dates of initiation (first patient enrollment) and completion (last patient's last observation), date of any early termination, and the date of the report.

2. Table of contents for the study

   The table of contents for the study should include volume and page number of each major part, including tabulations and case report forms. It should provide a list of appendices, if any, and of any tables separated from the text of the report.

3. Identity of the test materials, lot numbers, etc.

   For long-duration trials of test materials with limited shelf-lives, the logistics of resupply of the materials should be described. Any use of test materials past their expiration date should be noted, and patients receiving them identified. Any modifications of active control drugs from their usual commercial state should be noted (e.g., grinding a tablet and placing it in a capsule to facilitate blinding) and steps taken to assure that its clinical performance is unaltered noted.

4. Introduction

   The introduction should contain a brief statement of general intent and design of the trial. It should provide brief background information to place the study in proper context within the drug's clinical development and to indicate any special features or aims of the study.

5. Study objectives

   A statement of the specific objectives of the study should be provided. In addition to the primary objective, any secondary questions and subgroup hypotheses should be stated explicitly. It should be noted whether the objectives were pre-planned or formulated during or after completion of the study.

6. The investigational plan

   a. Overall design and plan of the study

      The overall study plan and design, and the organization of the study should be described briefly but clearly, using charts and diagrams as needed. The descriptions should include the treatments (specific drugs and doses) being compared; the patient population; the level and method of blinding (e.g., open, double-blind, single-blind, some blinded observers with other participants unblinded, etc.); the method of assignment of patients to treatment groups (e.g., randomization, stratification); the study configuration (parallel, crossover, etc.); and the sequence and duration of all study periods, including, as appropriate, a previous therapy withdrawal period, a baseline open or single-blind placebo period, the drug treatment period (sometimes including a titration and fixed dose period), a therapy withdrawal or post-treatment observation period, and any other defined period. It is usually helpful to display the design graphically (Appendix A, Figure 2, provides an example of a study flow chart showing doses, timing of clinic visits, and measurements at each visit). The actual protocol should be included as an appendix to the study report (Section III.B.13.c). Essential features of a protocol are discussed in Appendix C of the guideline and an example of a protocol cover sheet, which would enable the reviewer to quickly ascertain the principal features of the study design, is provided. If the study had an organizational structure in addition to the investigator (safety committee, data-monitoring committee, ECG committee, etc.), it should be described.

If other submitted studies used an essentially identical protocol, this should be noted and any differences described. It may be possible in that case to eliminate most of the description of the investigational plan.

If there was no written protocol for the study, there should be a detailed description of how the details of study design and conduct were determined.

Any important change in the protocol or conduct of the study made after the study was initiated should be described and its implications considered. Such changes could include dropping a treatment on the basis of intolerance or an interim analysis showing lack of effectiveness, altering the dose or dosing regimen, altering entry criteria, etc. These changes should be described briefly in this section and more fully in other sections where appropriate.

b. Description and discussion of the design and choice of control group(s)

The specific control chosen and the study design used should be discussed, as necessary. Generally, the control (comparison) groups that are identified in regulations are placebo concurrent control, no treatment concurrent control, active treatment concurrent control, dose comparison concurrent control, and historical control. These controls are described further in 21 CFR 314.126. In addition to the type of control, other critical design features that may need discussion are use of a crossover design and selection of patients with particular prior history, such as response or non response to a particular drug.

Known or potential problems associated with the design chosen, and its suitability for the specific claims under study, should be discussed. For example, for a crossover design, there should be consideration of the likelihood of spontaneous changes in the disease during the study, and the need (or lack of need) for reestablishment of baseline between treatment periods, or a plan to estimate residual effects to show that they are inconsequential. For a positive (active) control study, there should be evaluation of the appropriateness of the control and of the dose employed (e.g., regulatory approval of the treatment for the condition studied, literature support for effectiveness), and of whether the study was intended to show a difference between treatments or show similarity between them; if intended to show the latter, the present study design and patient population should be compared with previous studies of the control agent that were successful in showing effectiveness compared to placebo. Problems associated with the use of positive control study designs to demonstrate equivalence of a new drug to a standard agent have been considered in detail in recent publications: Temple R: "Government Viewpoint of Clinical Trials," DIA Journal: January/June 1982; Temple, R: "Difficulties in Evaluating Positive Control Trials," American Statistical Association: August 1983, pp. 1-7. The limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, etc.) and deserve particular attention.

Other specific features of the design may also deserve discussion, including presence or absence of washout periods and the duration of the treatment period, especially for a chronic illness. The rationale for dose and dose-interval selection should be explained, if it is not obvious. For example, once daily dosing with a short half-life drug whose effect is closely related in time to blood level is not usually effective; if the study design uses such dosing, this should be explained, e.g., by pointing to pharmacodynamic evidence that effect is prolonged compared to blood levels, and the procedures used to seek "escape" from drug effect at the end of the dose-interval, such as measurements of effect just prior to dosing, should be described. Similarly, in a parallel design dose-response study, the choice of doses should be explained.

c. Study population

The patient population and the selection and exclusion criteria used to enter the patients into the study should be described, and the suitability of the population for the purposes of the study discussed. Specific diagnostic criteria used, as well as specific disease requirements (e.g., disease of a particular severity or duration, results of a particular test or physical examination, or particular features of clinical history, such as failure or success on prior therapy), should be presented.

If there are both screening criteria and new criteria for randomization or entry into the drug treatment part of the trial, these should be described.

The planned sample size and the reasons for choosing it should be provided, including statistical considerations, practical limitations, etc.

d. Method of assigning patients to treatment

The specific means of assigning patients to treatment groups should be explicitly described, including any stratification or blocking procedures. A detailed description of the randomization scheme, including how it was executed, should be given in an appendix with references cited if necessary. A table exhibiting the randomization codes, patient identifier, and treatment assigned should be presented in the appendix. For a multicenter study, the table should be given by center. If the random numbers were generated by a computer, the seed number used should be indicated.

If randomization is not used, it is important to explain how other techniques, if any, guarded against systematic selection bias.

For a historically controlled trial, it is important to explain how the particular control was selected and what other historical experiences were examined, if any, and how their results compared to the control used.

e. Dose selection

Describe procedures for assigning the dose of test drug and control agent. These procedures can vary from simple random assignment to a selected fixed drug/dose regimen, to some specified titration procedure, to more elaborate response-determined selection procedures, e.g., where dose is titrated upward at intervals until intolerance or some specified endpoint is achieved. Procedures for back-titration, if any, should also be described.

The precise treatment (drug, control) used during study periods of the study (placebo baseline, randomized treatment, withdrawal, etc.) should be completely clear.

The timing of dosing in relation to meals should be described, if specified, and, if it was not specified, this should be noted.

f. Blinding

A description of the specific procedures used to carry out blinding should be provided (e.g., how bottles were labeled, double dummy techniques), including the circumstances in which the blind would be broken for individual or all patients, and who had access to patient codes. If the study allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Measures taken to assure that drug and placebo are indistinguishable should be described, and the appearance, shape, smell, and taste of the test materials should be described.

If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained; e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias. If blinding is considered desirable but not feasible, the reasons and implications should be discussed. Sometimes blinding is attempted but is known to be imperfect because of obvious drug effects in at least some patients (dry mouth, bradycardia). Such problems or potential problems should be identified and if there were any attempts to assess the magnitude of the problem or manage it (e.g., by having some measurements carried out by people unfamiliar with the clinical status of the patient), they should be described.

g. Effectiveness and safety variables recorded and data quality assurance

The specific effectiveness and safety variables recorded and laboratory tests conducted, their schedule (days of study, time of day, relation to meals, and the timing of critical measurements in relation to test drug administration, e.g., just prior to dosing), and the methods for measuring them should be provided. It is usually helpful to display graphically the frequency and timing of effectiveness and safety measurements; visit numbers and times should be shown, or, alternatively, times alone can be used (visit numbers alone are more difficult to interpret). See Appendix A, Figure 2. Any important instructions to the patient should be noted.

The means of obtaining adverse event data should be described (volunteered, checklist, questioning), as should any specifically planned follow-up procedures for adverse events or any planned rechallenge procedure. Any rating of adverse effects by the investigator or sponsor (e.g., severity rating, likelihood of drug causation) should be described and criteria for such ratings, if any, given.

If effectiveness or safety is to be assessed in terms of categorical ratings, numerical scores, etc., the criteria used for point assignment (e.g., definitions of point scores) should be provided. Similarly, any definitions used to characterize outcome (e.g., criteria for determining occurrence of acute myocardial infarction, designation of the location of the infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between TIA and stroke, assignment of cause of death) should be explained in full.

Any steps taken at the investigation site or centrally to assure accurate, consistent, complete, and reliable data, such as training sessions, monitoring of investigators by sponsor personnel, instruction manuals, data verification, cross-checking, use of a central laboratory for certain tests, centralized ECG reading, or audits based on probability sampling methods, should be described. For multicenter trials, it should be noted whether investigator meetings or other steps were taken to prepare investigators and standardize performance.

If anyone other than the investigator was responsible for evaluation of clinical outcomes (e.g., a committee to review x-rays or ECG's or to determine whether the patient had a stroke, acute infarction, or sudden death) the person or group should be identified and procedures, including means of maintaining blindness, described fully.

h. Compliance with dosing regimens

Steps to document patient compliance (pill counts, blood or urine levels, etc.) should be described.

i. Appropriateness and consistency of measurements

If any of the effectiveness or safety assessments is not standard, i.e., widely used and generally recognized as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents), its reliability, accuracy and relevance should be documented. It may be helpful to describe alternatives considered but rejected.

j. Criteria for effectiveness

The primary measurements and endpoints used to determine effectiveness should be clearly specified. Although the critical effectiveness measurements are often obvious, when there are multiple variables, or when variables are measured repeatedly, the protocol should identify the primary ones, with an explanation of why they were chosen, or designate the pattern of significant findings that would be interpreted as supporting effectiveness. If the protocol did not identify the primary variables, the study report should explain how these critical variables were selected (e.g., by reference to publications or past FDA action) and when they were identified (i.e., before or after the study was completed), and discuss the need, or lack of need, for statistical adjustments of type I error criteria for multiple comparisons.

k. Concomitant therapy

Describe which drugs were allowed during the study, how their use was recorded, any other specific rules and procedures related to concomitant therapy, and why allowed concomitant therapy would not be expected to confound treatment effect due to drug-drug interaction or how their independent effects could be ascertained.

l. Removal of patients from the study or analysis

The predetermined reasons for removing patients from therapy, if any, should be described, as should the nature and duration of follow-up procedures. In addition, any pre-set rules regarding which patients are "evaluable" should be described. If decisions about evaluability are made after blinding is broken, this should be noted specifically, and the potential bias introduced thereby discussed.

7. Statistical methods planned in the protocol

a. Statistical and analytical plans

Describe the planned statistical analyses and any changes made during or after the conduct of the study. In this section emphasis should be on which analyses and comparisons were planned, not on the specific statistical techniques used. If critical measurements were made more than once, the particular measurements (e.g., average measurements over the entire study, values at particular times, values only from study completers, or last on-therapy value) planned as the basis for comparison of drug and control should be specified. If there were any planned reasons for excluding from analyses patients for whom data are available, or any subgroups whose results were to be examined separately, these should be identified. If categorical responses (globals, severity scores, responses of a certain size) are to be used in analyzing responses, they should be clearly defined.

Planned monitoring of the results of the study should be described. If there is a data monitoring committee, either within or outside the sponsor's control, its composition and operating procedures should be described and procedures to maintain study blinding should be given. The frequency and nature of any planned interim analyses, any specified circumstances in which the study would be terminated, and any statistical adjustments to be employed because of interim analyses should be described.

b. Statistical determination of sample size

The planned sample size and the basis for it, such as statistical considerations or practical limitations, should be provided. Formulae for sample size and power calculation should be given together with their derivations or source of reference. Estimates used in the formulae should be given and explanations provided as to how they were obtained.

For a positive control study intended to show that a new therapy is at least as effective as the standard therapy, the sample size determination should specify a "delta value," a difference between treatments that would be considered clinically meaningful. A difference smaller than this delta would therefore indicate that the new therapy was clinically equivalent to the standard therapy. The power to detect a treatment difference of magnitude delta or greater (see Tables 5 and 6 in Appendix A for illustrations) should be given.

8. Disposition of patients entered

There should be a clear accounting of all patients who entered the study. The numbers of patients who entered and completed each phase of the study, or each week/month of the study (a flow chart is often helpful; see Table 7 in Appendix A), should be provided, as well as the reasons for all post-randomization discontinuations, grouped by treatment assignment and by major reason (lost to follow up, adverse experience, poor compliance, etc.). There should also be a patient-by-patient listing, by treatment group, giving a patient identifier, the reason for leaving, the treatment (drug and dose), and the duration of treatment before participation ended (see Table 8 in Appendix A for illustration). Whether or not the blind for the patient was broken at the time he left the study should be noted. It may also be useful to include other information, such as critical demographic data (age, sex), concomitant medication, and the major response variable(s) at termination.

For a multicenter study, these data should be displayed by center.

9. Efficacy results

a. Data sets analyzed

Exactly which patients are included in the effectiveness analysis should be precisely defined, e.g., all patients with any effectiveness observation or with a certain minimum number of observations, only patients completing the trial, all patients with an observation during a particular time window, only patients with a specified degree of compliance, etc. It should be clear, if not defined in the study protocol, when, relative to study completion, and how, inclusion/exclusion criteria were developed. As a general rule, even if the applicant's preferred analysis is based on a reduced subset of the patients with data, there should be an additional "intent-to-treat" analysis using all randomized patients.

There should be a tabular listing of all visits excluded from the effectiveness analysis (see Table 9 in Appendix A for an illustration). The reasons for exclusions should also be analyzed for the whole treatment group over time (see Table 10 in Appendix A).

b. Demographic and baseline features of individual patients and comparability of treatment groups

The critical demographic and baseline characteristics of the patients, as well as other factors arising during the study that could affect response, should be presented, and comparability of the treatment groups for each relevant characteristic should be documented by use of tables or graphs. If the data sets in the "intent-to-treat" analysis and the applicant's preferred analysis are substantially different, comparability of treatment groups in both sets should be examined and any other reasons for such differences should be discussed. The critical variables will depend on the specific nature of the disease, but will usually include demographic variables like age, sex, race, and weight; disease factors such as specific entry criteria (if not uniform), the duration and severity of the disease, and the baseline values for the critical clinical measurements carried out during the study; concomitant illnesses such as renal disease, diabetes, or heart failure; and concomitant treatment maintained, varied, or added during the study. In a multicenter study comparability should be assessed by center and the centers should also be compared.

In addition to tables and graphs representing group data for these baseline variables, individual patient demographic and baseline data and all concomitant medications taken should be presented in tabular listings. The applicant must decide which demographic and baseline information belongs in the full report of the study (as an appendix to the study report) and which can be included in the case report tabulations (21 CFR 314.50(f)); if in doubt, the applicant should discuss the matter with the reviewing FDA division, but ordinarily the full report should include at least the critical variables mentioned above, with specific baseline laboratory values where appropriate, listed by patient, within treatment group, and by investigator, if more than one, and including all patients randomized. An illustration of such a table is given in Appendix A, Table 11.

c. Analysis of each effectiveness measure and tabulation of individual patient data

1) Analysis of measures of effectiveness

Treatment groups should be compared for critical measurements of effectiveness. In general, results of all analyses contemplated in the protocol should be presented using tables and graphs to facilitate presentation.

Analyses based on continuous variables (e.g., mean blood pressure or depression scale score) and categorical responses (e.g., proportion of patients achieving cure of an infection) can be equally valid; ordinarily both should be presented if both were planned and are available. Even if one variable (e.g., in a blood pressure study, supine blood pressure at week x) receives major attention, other reasonable measures (e.g., standing blood pressure and blood pressures at other particular times) should be assessed, at least briefly. In addition, the time course of response should be analyzed, if possible. For a multicenter study, data display and analysis of individual centers should be included to give a clear picture of the results at each site, especially the larger ones. If any critical measurements or assessments have been made by more than one group (e.g., both the investigator and an expert committee may offer an opinion on whether a patient had an acute infarction), overall differences between the ratings should be shown, and each patient having disparate assessments should be identified. The assessments utlized should be clear in all analyses.

2) Statistical/analytical issues

The statistical analysis used should be described, with detailed documentation of statistical methods presented in an appendix (see Section III.B.9.d). Important features of the analysis, such as the particular tests used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of drop-outs and missing data, adjustments for multiple comparisons, special analyses of multicenter studies, and adjustments for interim analyses, should be discussed.

a) Adjustments for covariates

Selection of, and adjustments for, demographic or baseline measurements, concomitant therapy, or any other covariate or prognostic factor should be explained in the report, and methods of adjustment, results of analyses, and supportive information (e.g., ANCOVA or Cox regression output) should be included in the detailed documentation of statistical methods. Information for individual studies presented in Tables 12 and 13 would be useful for documenting these types of adjustments in the individual study reports; in addition, comparisons of effects of various prognostic variables as illustrated in these tables would be useful in the Integrated Summary of Effectiveness Data for Controlled Studies (see Section II.G.2.b of this Guideline).

b) Handling of dropouts or missing data

There are several factors that may affect dropout rates. These include the duration of the study, the nature of the disease, the effectiveness and toxicity of the drug under study, and other factors that are not therapy related. Ignoring the patients who dropped out of the study and drawing conclusions based only on patients who completed the study can be misleading, but a large number of dropouts, even if included in an analysis, may introduce bias, particularly if there are more early dropouts in one treatment group. While the effects of early dropouts, and sometimes even the direction of bias, can be difficult to determine, possible effects should be explored as fully as possible. It may be helpful to examine the observed cases at various time points or, if dropouts are very frequent, to concentrate on analyses at time points when most of the patients are still under observation and when the full effect of the drug has been realized.

The results of a clinical trial should be assessed not only for the subset of patients who completed the study, but also for the entire patient population randomized (the intent-to-treat analysis). Several factors need to be considered and compared for the treatment groups in analyzing the effects of dropouts: the reasons for the dropouts, the time to dropout, and the proportion of dropouts among treatment groups at various time points.

Procedures for dealing with missing data, e.g., use of imputed data, should be described. Detailed explanation should be provided as to how such imputations were done and what underlying assumptions were made.

c) Interim analyses and data monitoring

The process of examining and analyzing data accumulating in a clinical trial, either formally or informally, can introduce bias. Therefore, all interim analyses, formal or informal, by any study participant, sponsor staff member, or data monitoring group should be described in full, even if the treatment groups were not identified. The need for statistical adjustment because of such analyses should be addressed. Minutes of meetings of a data monitoring group may be useful (and may be requested by the review division).

d) Multicenter studies

A multicenter study is a single study involving several centers (or investigators) where the data collected from these centers are intended to be analyzed as a whole (as opposed to a post-hoc decision to combine data or results from separate studies). Individual center results should be presented, however, and statistical tests for homogeneity across centers, i.e., for detecting treatment-by-center interaction, should be provided. The significance level used to declare the significance of a given test for treatment by center interaction should be considered in light of the sample sizes involved. Any extreme or opposite results among centers should be noted and discussed. As mentioned in previous sections, demographic, baseline, and post-baseline data, as well as efficacy data, should be presented by center, even though the combined analysis is the primary one. Figure 1 in Appendix A with study # replaced by center on the X-axis is a display of individual center results with associated 95%-confidence intervals.

e) Multiple endpoints

False positive findings increase in frequency as the number of significance tests (number of comparisons) performed increases. If there is more than one primary endpoint (outcome variable), or if there are multiple treatment groups, or subsets of the patient population being examined, statistical analysis should reflect awareness of this and either explain the statistical adjustment used for type I error criteria or give reasons why they are considered unnecessary.

f) Use of an "efficacy subset" of patients

Particular attention should be devoted to the effects of dropping patients with available data from analyses because of poor compliance, missed visits, or any other reason, and, as noted above, an analysis using all available data should be carried out, even if it is not the analysis preferred by the applicant.

g) Active-control studies

If the trial is an active-control study intended to show equivalence between the test drug and active control, there should be assessments of (1) the response of the standard agent in the present trial compared to previous studies of similar design that included comparison with placebo and (2) the ability of the study to have detected differences between the treatments of a defined size, e.g., by providing confidence limits for the difference between the drug and active control and/or the power to detect a difference between the treatments of specified size.

3) Examination of subgroups

If the size of the study permits, relevant demographic or baseline value-defined subgroups should be examined for unusually large or small responses and the results presented, e.g., comparison of effects by severity groups, by age, sex, or race, or by history of prior treatment with a drug of the same class. These analyses are not intended to "salvage" an otherwise non-supportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labeling information, patient selection, dose selection, etc.

4) Tabulation of individual response data

In addition to tables and graphs representing group data, individual response data and other relevant study information should be presented in tables. What needs to be included in the report will vary from study to study and from one drug class to another and the applicant must decide, preferably after consultation with the relevant review division, what to include in the full report (as an appendix to the study report) and what to leave for case report tabulations (21 CFR 314.50(f)). (The full report should indicate what material is included as an appendix and what is in case report tabulations.)

For a controlled study in which critical effectiveness measurements or assessments (e.g., blood or urine cultures, pulmonary function tests, angina frequency, or global evaluations) are repeated at intervals, the case report tabulations should include, for each patient, a patient identifier, all measured or observed values of critical measurements, including baseline measurements, with notation of the time during the study (e.g., days on therapy and time of day, if relevant) when the measurements were made, the drug/dose at the time (it is useful to give as mg/kg), and any concomitant medications at the time of, or close to the time of, measurement or assessment. If, aside from repeated assessments, the study included some overall evaluation(s) (responder vs. non-responder, bacteriologic cure or failure), it should also be included. In addition to critical measurements, the tabulation should note whether the patient is included in the effectiveness evaluation (and which evaluation, if more than one), provide patient compliance information, if collected, and a reference to the location of the case report form, if included. Critical baseline information such as age, sex, weight, disease being treated (if more than one in study), disease stage or severity, and causative pathogen is also helpful. The baseline values for critical measurements would ordinarily be included as zero time values for each effectiveness measurement.

The tabulation described usually should be included in the full report of the study, rather than in the case report tabulations, because it represents the basic effectiveness data supporting summary tables. Such a thorough tabulation can be unwieldy for review purposes, however, and it is expected that more targeted displays will be developed as well. If there are many measurements reported, tabulations of the most critical measurements for each patient (e.g., the blood pressure value at certain visits might be more important than others) will be useful in providing a rapid overview of each individual's results in a study, with each patient's response summarized on a single line or small number of lines.

d. Documentation of statistical methods

1) Statistical considerations

Details of the statistical analysis performed on each primary efficacy measure should be presented in the appendix [Section III.B.13.f, expanding on the description provided in Section III.B.9.c.2)]. Details reported should include at least the following information:

a) The statistical model underlying the analysis. This should be presented precisely and completely, using references if necessary.

b) A statement of the clinical claim tested in precise statistical terms, e.g., in terms of null and alternative hypotheses.

c) When statistically reasonable and appropriate, the power against specific clinically meaningful alternatives for those tests that fail to reject the null hypothesis to indicate whether the study size was adequate. In addition, in an active control study if a substantial number of patients were not included in a given analysis for reasons such as dropout or non-evaluability, then a post-study calculation of the power of the test to detect a meaningful treatment difference, usually called the "delta value" (this "delta value" should have been specified in the protocol), should be provided.

d) The statistical methods applied to estimate effects, construct confidence intervals, etc. Literature references should be included (Section III.B.12), where appropriate.

e) The assumptions underlying the statistical methods. It should be shown, insofar as statistically reasonable, that the data satisfy crucial assumptions, especially when necessary to confirm the validity of an inference. When extensive statistical analyses have been performed by the applicant, it is essential to consider the extent to which the analyses were planned prior to the availability of data and, if they were not, how bias was avoided in choosing the particular analysis used as a basis for conclusions. This is particularly important in the case of any subgroup analyses, because if such analyses are not pre-planned they will ordinarily not provide an adequate basis for definitive conclusions.

(1) Unnecessary data transformation should be avoided. In the event data transformation was performed, a rationale for the choice of data transformation along with the interpretation of the estimates of treatment effects based on transformed data should be provided.

(2) A discussion of the appropriateness of the choice of statistical procedure and the validity of statistical conclusions will guide the FDA statistical reviewer in determining whether reanalysis of data is needed.

(3) Only appropriate statistical methods should be used; using many methods for the same data is not appropriate. For similar protocols the method applied should be the same.

f) The test statistic, the sampling distribution of the test statistic under the null hypothesis, the value of the test statistic, significance level (i.e., p-value), and intermediate summary data, in a format that enables the FDA statistical reviewer to verify the results of the analysis quickly and easily. The p-values should be designated as one- or two-tailed. The rationale for using a one-tailed test should be provided.

For example, the documentation of a two-sample t-test should consist of the value of the t-statistic, the associated degrees of freedom, the p-value, the two sample sizes, mean and variance for each of the samples, and the pooled estimate of variance. The documentation of multi-investigator studies analyzed by analysis of variance techniques should include, at a minimum, an analysis of variance table with terms for investigators, treatments, their interaction, error, and total. For crossover designs, the documentation should include information regarding sequences, patients within sequences, baselines at the start of each period washouts and length of washouts, dropouts during each period, treatments, periods, treatment by period interaction error, and total. For each source of variation, aside from the total, the table should contain the degrees of freedom, the sum of squares, the mean square, the appropriate F-test, the p-value, and the expected mean square. Generally, it is recommended that SAS Type III or equivalent analyses be provided in addition to any other analyses.

Intermediate summary data should display the demographic data and response data, averaged or otherwise summarized, for each investigator-by-treatment combination (or other design characteristic such as sequence) at each observation time.

2) Format and specifications for submission of data requested by FDA's statistical reviewers

In the report of each controlled clinical study, there is a requirement for data listings (tabulations) of patient data utilized by the sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the FDA statistical review, and the sponsor may be asked to supply these patient data listings in a computer-readable form, preferably on floppy diskettes or on magnetic tapes. In addition, patient data so submitted should be in a format readily acceptable for use on the FDA computers. Guidance on how to provide these data is provided in Appendix B.

e. Analysis of doses administered and, if possible, dose-response and blood level-response relationships

Unless the study involved fixed doses, the actual doses received by patients should be shown and individual patient's doses should be tabulated. While many studies cannot provide dose-response information because time effects cannot be distinguished from dose effects as patients are titrated, or because only poorly responsive patients are given the larger doses, the available data should be examined for whatever information they can yield. In examining the dose-response, it is helpful to calculate dose as mg/kg body weight. Blood level information, if available, should also be related to response.

f. Analysis of drug-drug and drug-disease interactions

Any relation of response to concomitant therapy or concomitant illness should be noted.

g. By-patient displays

While individual patient data ordinarily can be displayed in tabular listings, with patients and each measurement date in columns and the collected data in rows, it has on occasion been helpful to construct individual patient profiles in other formats, such as graphic displays. These might, for example, show the value of a particular parameter(s) over time, the drug dose over the same period, and the times of particular events (e.g., an adverse reaction or change in concomitant therapy). Where group mean data represent the principal analyses, this kind of "case report extract" may offer little advantage; it may be helpful, however, if overall evaluation of individual responses is a critical part of the analysis.

10. Safety results

a. Extent of exposure

The extent of exposure to study drugs (and placebo, if any) (number of patients exposed, duration of exposure, and dose) should be described. While mean exposure may be helpful, it is also valuable to describe exposure in reasonable categories, e.g., one day or less, two days to one week, more than one week to one month, as appropriate to the drug class. In some cases it may be useful to display dose exposure as mg/kg dose. The duration of post-treatment follow-up should also be described. It is assumed that all patients entered into treatment who received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

b. Adverse experiences

1) The overall adverse event experience in the study should be described in a brief narrative, supported by the following more detailed tabulations and analyses. In all tabulations and analyses events associated with both test drug and control drug should be displayed.

2) Display and analysis of all adverse events and occurrence rates

All new adverse events (i.e., those not seen at baseline or worsened even if present at baseline), which are sometimes called treatment emergent signs and symptoms (TESS), should be displayed in tables listing each reported adverse event, the number of patients in each treatment group in whom the event occurred, and the rate of occurrence in each treatment group. Adverse events should be grouped by body system and each event should be divided into defined severity categories (e.g., mild, moderate, severe) if these were used. The tables can also divide the adverse events into those considered related to drug use and those considered not related, or use some other causality scheme (e.g., remote, possible, probable, definite). For any such categorization, the categories should be defined. Even when such a causality assessment is used, the tables should include all adverse events, whether or not considered drug related, including events thought to represent intercurrent illnesses. Subsequent analyses may distinguish between adverse events that are, or are not, considered drug related.

So that it is possible to analyze and evaluate the data in these tables, it is useful to identify each patient having each adverse event, as grouped in the table, by individual patient number, for some or all of the controlled trials (which studies to display in this fashion should be discussed with the reviewing division). An example of such a tabular presentation is shown below:

Adverse Reaction: Number Observed and Rate, with Patient Identifications

Treatment Group X N=50

	Mild*		Moderate		Severe		Total	
	Related	NR	Related	NR	Related	NR	Related	NR
Body System A								
Event 1	6(12%)	2(4%)	3(6%)	1(2%)	3(6%)	1(2%)	12(24%)	4(8%)
	N11**	N21	N31	N41	N51	N61		
	N12	N22	N32		N52			
	N13		N33		N53			
	N14							
	N15							
	N16							
Event 2								

*NR = not related; this could be expanded, e.g., as definite, probable, possible

**Patient identification number

If this presentation is utilized, it may be useful also to provide the table without the patient identifying numbers for quicker reference; treatment and control groups could be shown on the same page. If both tables are used, the latter should be included in the main report, the former in an appendix.

In some cases it is useful to give the number of patients who had any adverse event or no adverse event. Patient identification numbers need not be listed for these categories.

3) Grouping adverse event terms that probably represent the same event

It is important, in presenting adverse events, both to display the original terms used by the investigator and to attempt to group related reactions (i.e., events that probably represent the same phenomena) so that the true occurrence rate is not obscured. One way to do this is with a standard adverse reaction dictionary, but experience at this time is too limited to recommend a particular one for this purpose. In general, the individual study report should emphasize the reported terminology, leaving use of a standard dictionary for the integrated summary of safety data. Nonetheless, probably synonymous reactions should be grouped (e.g., heartburn, indigestion, or dyspepsia).

4) Analysis of adverse events

The basic display of adverse event rates described above should be used to compare rates in treatment and control groups. In addition, if study size permits, the more common adverse events that seem to be drug related should be examined for relationship to dosage and to mg/kg dose, to dose regimen, to duration of treatment, to total dose, to demographic characteristics, such as age, or to other baseline features, such as renal status, and to blood level, if data are available. A variety of additional analyses may be suggested by the study results or by the pharmacology of the drug.

It is not intended that every adverse event be subjected to rigorous statistical evaluation. It may be apparent from initial display and inspection that a significant relation to demographic or other baseline features is not present. Adverse events that are relatively important (those that lead to discontinuation or dose changes or are characterized as severe) deserve closest attention. Consultation with the reviewing division is encouraged if questions arise about the kind of analysis needed.

If the individual studies are small, it may be more useful to reserve analyses other than the comparison of treatment and control for the integrated summary of safety data.

Under certain circumstances, the standard life table method analysis may be more informative than reporting of crude adverse event rates.

5) Listing of each patient's adverse event(s)

All adverse events for each patient, including the same event on several occasions, should be listed using the terminology supplied by the investigator. Laboratory findings that constitute an adverse event (ECG abnormality suggesting infarction, serious arrhythmia, etc.) should be included. Ordinarily, this listing should be included in the case report tabulations section [21 CFR 314.50(f)], but it could be included instead as an appendix to the study report. The listing should be by investigator (if more than one), and by treatment group, and should include:

- patient identifier
- age, sex, race, weight
- treatment and dose and mg/kg dose at time of adverse experience
- compliance measure, if available
- date of onset, if known, or clinic visit at which event was discovered
- duration of treatment at time of adverse experience
- the adverse experience
- duration of adverse experience
- intensity (e.g., mild, moderate, severe)
- action taken (none, change in dose, therapy interrupted or stopped, etc.)
- outcome (e.g., recovered, no residual effect; persistent but no treatment; persistent and being treated; residual effect being treated; residual effect, no treatment; death)
- relationship to test drug (how this is determined should be explained in the table or elsewhere)
- location of case report form, if provided

For the table to be of reasonable size it will be necessary to use some abbreviations and codes. These should be clearly explained at the beginning of the listing, or, even better, on each page. For an example of a table, see Table 14 in Appendix A.

6) Display and analysis of deaths and dropouts due to adverse events (adverse dropouts) and other adverse events that are serious or potentially serious.

There should be listed all patients who left the study prematurely because of an adverse experience, including a laboratory abnormality that led the investigator to terminate participation, but not including instances of therapeutic failure. The listing should include a patient identifier and the same information as called for in section 5) above, as well as the location of the case report, and this listing should be part of the report, not placed in the tabulations section. A similar table should be prepared for patients requiring dose reduction or institution of concomitant therapy because of an adverse event.

All deaths during, or within a short period after, the study should be similarly listed.

If there were other serious adverse events, not included among patients who died, left the study, or had a dosage adjustment, these should also be listed.

For all deaths and all potentially serious adverse experiences, there should be a brief narrative describing each event and assessing the likelihood that the drug was responsible. Whether an adverse experience is potentially serious is a matter of judgment, and the basis for the judgment should be explained.

The significance of the fatalities and adverse dropouts should be assessed, particularly with respect to whether any of these events may represent a previously unsuspected important adverse effect of the drug.

For serious events that appear of particular importance, it may be useful to utilize life table approaches to show their relation to time on drug and to assess their risk over time. Ordinarily, however, rates of such events will be so low that such an analysis should be reserved for the Integrated Summary of Safety Information Section.

c. Clinical laboratory evaluation

1) Listing of individual laboratory measurements by patient

The results of all safety-related laboratory tests carried out on every patient should be provided in tabular listings, unless the agency has agreed in advance that a particular tabulation is not pertinent to a review of the drug's safety. These tabulations should, in general, be placed in the "Case Report Tabulations" section of the NDA, unless the applicant has reason, or is asked by the agency, to place certain of them elsewhere.

In these tabulations, each row should represent a patient visit at which a laboratory test was run with patients grouped by study, and within a study by investigator (if more than one), and by treatment group. Within each treatment group, patients generally should be listed in numerical order of patient identifier number. The tabulations should then provide a few columns of critical information about each patient, such as the visit or number of days into study period at the time of examination and drug dose (total and mg/kg), if this is variable, at the time of testing. Age, sex, and weight can also be provided although this may be available readily from other near-at-hand tabulations. The remainder of the tabulation should consist of columns giving the results of each laboratory test, one column per test, as shown on the next page:

							Laboratory Tests		
Patient	Time	Age	Sex	Race	Weight	Dose	SGOT	SGPT	AP......X
#1	0	70	M	W	70 kg	400 mg	V1*	V5	V9
	1						V2	V6	V10
	2						V3	V7	V11
	3						V4	V8	V12
#2	0	65	F	B	50 kg	300 mg	V13	V16	V19
	1						V14	V17	V20
	2						V15	V18	V21

* Vn = value of a particular test

How many tests can be displayed in a single table will be variable but as many as possible should be included consistent with legibility, so that as complete as possible a view of each patient's laboratory experience can be encompassed by a single look at the data. If several tables are needed, tests should be grouped logically, e.g., hematologic tests together, tests of liver function together, and tests of renal function, urinalysis, and electrolytes together.

Normal laboratory ranges should be readily available at the beginning of tabulations or at the head of each page and differences among laboratories should be noted.

Some means should be devised for identifying all abnormal values, such as underlining, brackets, or asterisks, etc.

2) Listing of each abnormal laboratory value

While the complete record of laboratory tests should be included in the Case Report Tabulations, a by-patient listing of all abnormal values should be included with the full report of the study, generally as an appended table. Format is generally as above, with patients' visits representing rows and laboratory tests the columns.

It may be desirable to exclude certain abnormal values from this listing. For example, single, non-replicated, small abnormalities of some tests (e.g., uric acid or electrolytes) or occasional low values of some tests (e.g., transaminase, alkaline phosphatase, BUN, etc.) can probably be defined as insignificant clinically and excluded. Any such decisions should be clearly explained, however, and the complete list of values provided in 1) above should identify every abnormal value.

Normal values for the laboratory carrying out each test should be provided.

3) Evaluation of each laboratory parameter

The necessary evaluation of lab values must in part be determined by the results seen, but, in general, the following analyses should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as compatible with study size. In addition, normal laboratory ranges should be given for each analysis.

a) Mean (median) values over time

Mean (or median if more appropriate) values of each parameter over the course of the study (e.g., at each visit), as well as the range of values and the number of patients with abnormal values, or with abnormal values that are of a certain size, e.g., twice the upper limit of normal, 5 times the upper limit, etc. Graphs may be used.

b) Individual patient changes

Analysis of individual patient changes by group. A variety of approaches have been used, including:

i. "Shift tables" - These tables show the number of patients who are low, normal, or high at baseline and then at selected time intervals.

ii. Tables showing the number or fraction of patients who show a change in parameter of a predetermined size at selected time intervals. E.g., for BUN, it might be decided that a change of more than 10 mg/dL should be noted. For this parameter, the number of patients having a change less than this or greater than this would be shown for one or more visits, usually grouping patients separately depending on baseline BUN (normal or elevated). The possible advantage of this display, compared to the usual shift table, is that changes of a certain size are noted, even if the final value is not abnormal.

iii. A graph plotting the initial value for each patient on the abscissa and a subsequent value on the ordinate. If no change occurs, the patient will be located on the 45^0 line. A general shift to higher values will show a clustering of patients above the line. As this display can show only a single time point for a single treatment, interpretation requires a time series of these plots for treatment and control groups. This kind of display identifies outliers readily.

c) Individual marked abnormalities

Although minor transient changes may not warrant detailed discussion, marked changes (defined by the applicant) require separate discussion. While a narrative of each patient whose abnormality led to discontinuation of treatment should be provided under section III.10.b.6) above, marked changes that do not lead to discontinuation should also be discussed in narrative form. An analysis of these marked changes, together with a recapitulation of the discontinuations, should be provided for each parameter. The significance of the marked changes and likely relation to the treatment should be assessed, e.g., by analysis of such features as disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy.

11. Summary and conclusions

The effectiveness and safety results of the study should be briefly summarized, referring as needed to tables, figures, and sections above as needed; particular attention should be paid to unusual findings, such as inconsistencies among related measures or failure of the expected response or a particularly serious adverse experience that may, or may not be drug related. Limitations of the study, e.g., non-applicability to particular subgroups or subpopulations, if any, should be identified.

12. References

    A list of articles from the literature pertinent to evaluation of the study should be provided, and, if necessary, copies of important publications should be attached.

13. Appendices

    a. Cross-references of all pertinent materials

       A table cross-referencing all summary tables, figures, and graphs to relevant supporting data, including patient data listings, ANOVA tables, and other pertinent information, should be provided (see Table 15 in Appendix A for an illustration). Alternatively, and preferably, the sponsor may provide such information with each table.

    b. Protocol, sample case report form, and amendments [see Section II.D.2.c.2)]

    c. Publications based on part or all of the results of the study [see Section II.D.2.c.3)]

    d. List of investigators [see Section II.D.2.c.4)]

    e. Randomization scheme and codes (see Section III.B.6.d)

    f. Documentation of statistical methods (see Section III.B.9.d)

    g. Patient data listings (or reference to their location in the Case Report Tabulations)

       i. Demographic data

       ii. Individual effectiveness response data

       iii. Adverse reaction listings [see Section III.B.10.b.5)] and table of adverse event rates including patient numbers [see Section III.B.10.b.2)]

       iv. Listing of each abnormal laboratory value [see Section III.B.10.c.2)]

IV. CASE REPORT TABULATIONS [21 CFR 314.50(f)(1)]

The requirements for tabulations are described in the regulations [21 CFR 314.50(f)(1)].

A. Data to Be Tabulated

1. Effectiveness data from adequate and well-controlled trials, including all measurements made

2. Data from clinical pharmacology (phase 1) studies

3. Safety data (adverse events, laboratory data) from all studies

   Essentially all data of these types are to be tabulated except that the applicant and agency may agree to the deletion of particular tabulations not pertinent to the evaluation of safety or effectiveness. These tabulations are distinct from, and more extensive than, the tabulations of individual patient data called for as parts of the full reports of controlled clinical studies and the safety portions of reports of all studies. These case report tabulations contain, in an organized fashion, essentially all data (of the above three types) collected in the case report. Generally, the tabulations in study reports will be subsets of relevant effectiveness and safety variables used in analyses and tables. As in the tabulations in study reports, any unreported value should be clearly identified as such.

B. Format of Tabulations

1. General requirements

   As with all tables and graphs, headings should be clear and well-defined and the study they refer to specifically identified. As many columns as possible, consistent with legibility, should be included to allow comparison across variables. The usual presentation is by patient and, for each patient, by visit, with patients grouped by study, by investigator, and by treatment.

2. Specific requirements:

   a. Demographic and baseline information

      There should be tabular listings of each patient's baseline demographic features (age, sex, race, weight), the basis for including him in the study (entry criteria met), recorded features of the disease (duration, severity, prior treatment, etc.), concomitant illness, any drugs to be continued during the study, and any drugs added during the study. (Admission history forms may have many items not needed for evaluation; what to include should be discussed with the reviewing division.)

b. Measures of effectiveness

For controlled studies, tabulations should include all recorded measures, including questionnaire items, physical or electrical measurements (BP, EKG, Holter, electrocardiogram, x-ray, etc.), global ratings, and diary records, and should be presented with enough other information about the patient to allow measures to be interpreted, such as time of measurement and drug dose. [See III.B.9.c.4)]

c. Measures of safety

All adverse experiences and all laboratory measurements should be recorded as described in III.B.10.b.5) and c.1).

V. CASE REPORT FORMS [21 CFR 314.50(f)(2)]

As stated clearly in the regulations, 21 CFR 314.50(f)(2) and (3), only certain case report forms (CRF) will routinely be requested: those for any patient who died during a clinical study or who did not complete the study because of an adverse event, whether or not that event was believed to be drug related, including patients receiving reference drugs or placebo.

While not all CRF's will be required routinely, reviewers will usually need access to CRF's on the critical well-controlled studies. In order to choose these appropriately, and at a time when they can be provided without causing delay in review of the application, FDA reviewers will designate, approximately 30 days after receipt of an application, the critical studies for which case reports will be requested.

A description of an adequate case report form is beyond the scope of this document, except to observe that, in general, it should record clearly all demographic and diagnostic information, all dosing information with the study drug and other therapies, and all observations made. It should be possible to distinguish observations not made from those that are made but are "negative." One caveat seems in order. Efforts to make the forms as easy to analyze as possible have led to a substitution of checklists for narrative in many situations. Case report forms should retain room for spontaneous comments by the investigator, especially with respect to unusual responses and adverse experiences. The investigator should be free to use adverse experience terms he finds suitable and room on the form should be left for this. Common adverse experience terms can, of course, be listed, as well as any modifying statements that can help evaluate causality, severity, etc.

VI. THE ARCHIVAL COPY AND GENERAL CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS

A. The Archival Copy

Under the current regulations, the drug sponsor is required to submit a complete archival copy of the new drug application and a review copy to each one of six reviewing disciplines [21 CFR 314.50(h)]:

1. Chemistry, Manufacturing, and Control
2. Nonclinical Pharmacology and Toxicology
3. Human Pharmacokinetics and Biovailability
4. Microbiology
5. Clinical
6. Statistics

The purpose of the archival copy is to permit the individual reviewers to refer to information that is not contained in the review copies of their technical sections, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the entire application. The organization and content of the archival copy of an NDA is as outlined below [21 CFR 314.50(h)(1)]:

ARCHIVAL COPY OF A NEW DRUG APPLICATION

COVER LETTER
a. APPLICATION FORM (356H)
b. INDEX
c. SUMMARY
d. TECHNICAL SECTIONS

    1. CHEMISTRY, MANUFACTURING, AND CONTROL SECTION
    2. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION
    3. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION
    4. MICROBIOLOGY SECTION
    5. CLINICAL DATA SECTION
    6. STATISTICAL SECTION

e. SAMPLES AND LABELING
f. CASE REPORT FORMS AND TABULATIONS

B. Clinical and Statistical Sections

The review copies for the clinical and statistical reviewing disciplines should be separately bound, each containing a copy of the COVER LETTER, a copy of the INDEX, a copy of the SUMMARY, and a copy of their respective technical sections as outlined below:

Review Copy for the Clinical Reviewing Division

COVER LETTER
a. APPLICATION FORM (356H)
b. INDEX
c. SUMMARY
d.5 CLINICAL SECTION

Review Copy for the Statistical Reviewing Division

COVER LETTER
a. APPLICATION FORM (356H)
b. INDEX
c. SUMMARY
d.6 STATISTICAL SECTION

C. The COVER LETTER of an NDA

The review copies of an application for the clinical and statistical disciplines should include a copy of the COVER LETTER contained in the archival copy of the application. This cover letter: (i) confirms any agreements or understandings between FDA and the applicant; (ii) identifies one or more persons the agency may contact regarding the application; and (iii) conveys any other important information about the application.

This cover letter should identify the reviewing division including the HFD number to which the application is being submitted. If the letter is addressed to the director of a reviewing division, then an appropriate place for the HFD-number would be after the name of the director of that division. In addition to the cover letter, other relevant correspondence should also be included here. Letters of authorization may also be included here, if applicable.

D. The APPLICATION FORM (356h) of an NDA [21 CFR 314.50 (a)]

For a detailed description of the information needed for this form, the sponsor should refer to the Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications (pages 16-18).

E. The INDEX of an NDA [21 CFR 314.50(b)]

The archival copy of the application is required to contain a comprehensive index by submission number, volume number, and page number to the SUMMARY, the TECHNICAL SECTIONS, and all supporting information including SAMPLES AND LABELING [21 CFR 314.50(e)] and CASE REPORT FORMS AND TABULATIONS [21 CFR 314.50(f)]. If microfiche is used for portions of an application, the fiche number should also be given.

The index should identify the location of the major sections and subsections of the various technical sections and the location of each study report and summaries by submission number, volume number, and page number. It is most helpful if, where a section is omitted (e.g., if there are no uncontrolled studies), the listing is included anyway, labeled "not applicable." This index should be included in the clinical and statistical sections.

If the volume of the material permits it, the COVER LETTER, APPLICATION FORM, INDEX, and SUMMARY, should all be bound in a single volume. It is not necessary to include a copy of the INDEX at the beginning of every volume. It suffices to include a copy of the INDEX in the first (summary) volume.

F. The SUMMARY of an NDA [21 CFR 314.50(c)]

For a detailed discussion on the format and content of a SUMMARY, the applicant may refer to the Guideline for the Format and Content of the Summary for New Drug and Antibiotic Applications.

VII. OUTLINE OF THE CLINICAL AND STATISTICAL SECTIONS

CLINICAL SECTION

A. List of Investigators, List of IND's and NDA's (Section II.A)

B. Background/Overview of Clinical Investigations (Section II.B)

C. Clinical Pharmacology (Section II.C)

1. Table of all studies, grouped by study type

2. ADME studies (absorption, distribution, metabolism, excretion)

   a. Synopsis of each study
   b. Full report of each study
   c. Summary and evaluation of all studies

3. Early dose-tolerance studies

   a, b, c as above

4. Short-term studies of therapeutic response or of a pharmacodynamic effect thought to relate to therapeutic response, including dose-response and blood level-response studies

   a, b, c as above

5. Studies of pharmacodynamic properties other than the property thought to be related to clinical effectiveness

   a, b, c as above

6. "Special" studies

   a, b, c as above

7. Overall Summary of Clinical Pharmacology

D. Controlled Clinical Studies (Section II.D)

1. Table of all studies, grouped by indication, study design, completion status, location, and availability of case reports

2. Indication 1

   a. Placebo concurrent control studies

      1) Completed Studies

         a) Domestic, full case reports available

            (1) Study # 101

               i. Brief synopsis
               ii. Protocol
               iii. Related publication
               iv. List of investigators
               v. Integrated clinical and statistical report

            (2) Study #102, etc.

               i-v as above

         b) Foreign, full case reports available

            (1) Study # 201

               i-v as above

            (2) Study # 202, etc.

               i-v as above

         c) Published reports and other reports lacking full case reports

            (1) Study # 301

               i-v as appropriate

      2) Ongoing studies with interim results

         a)-c) as above

      3) Incomplete studies no longer active

         a)-c) as above

   b. Dose comparison concurrent control studies

      1)-3) as above

c. No treatment concurrent control studies

    1)-3) as above

d. Active treatment concurrent control studies

    1)-3) as above

e. Explicit historical control studies

    1)-3) as above

3. Indication 2 ... n

    a-e as above

4. Optional overall summary and evaluation of data from controlled trials

E. Uncontrolled Clinical Studies (Section II.E)

1. Table of all studies, grouped by indication, completion status, availability of case reports and location

2. Indication 1

    a. Completed studies

        1) Domestic, full case reports available

            a) Study # 401

                1) Brief synopsis
                2) Protocol
                3) Related publication
                4) List of investigators
                5) Report of the study

            b) Study # 402

                1)-5) as above

        2) Foreign, full case reports available

            a) and b) as above

        3) Published reports and other reports lacking full case reports

            a) and b) as above

- b. Incomplete studies
    - 1)-3) as above
- 3. Indication 2 ... n
    - a-b as above

F. Other Studies and Information (Section II.F)

- 1. Table of all studies
- 2. Controlled studies of uses other than those claimed in the application, any design, complete or incomplete
    - a. Studies with case reports available
        - 1) Study # 501
            - a) Brief synopsis
            - b) Protocol
            - c) Related publication
            - d) List of investigators
            - e) Report of the study
        - 2) Study # 502, etc.
            - a)-e) as above
    - b. Studies without case reports available
        - 1) and 2) as above
- 3. Uncontrolled studies of uses other than those claimed in the application
    - a. Studies with case reports available
        - 1) Study # 601
            - a) Brief synopsis
            - b) Protocol
            - c) Related publication
            - d) List of investigators
            - e) Report of the study
        - 2) Study # 602, etc.
            - a)-e) as above

b. Published reports and other reports without case reports available

1) and 2) as above

4. Commercial marketing experience

   a. List of countries in which drug has been approved
   b. Reports from regulatory authorities
   c. Epidemiologic studies
   d. Spontaneous reports from foreign marketing experience of serious adverse experiences

5. Reports from literature or elsewhere not otherwise reported

   a. Published case reports, letters, etc.
   b. Other information

G. Integrated Summary of Effectiveness Data (Section II.G)

1. Identification of studies fulfilling the statutory requirements for adequate and well-controlled studies showing that the drug has its intended effect

2. Comparison and analysis of all controlled trials

3. Results of uncontrolled studies, if pertinent

4. Analysis of dose-response or blood-level response information

5. Analysis of response in subsets of the overall population: drug-demographic, drug-drug, and drug-disease interactions

6. Evidence of long-term effectiveness, tolerance, and withdrawal effects

H. Integrated Summary of Safety Data (Section II.H)

1. Table of all investigations pertinent to safety, identified by protocol number and principal investigator, grouped by study type

2. Overall extent of exposure

3. Demographic and other characteristics of the study population

4. Adverse experiences in clinical trials
    a. Narrative summary of adverse event experience
    b. Display of adverse events and occurrence rates
    c. Analysis of adverse event rates
    d. Display and analysis of deaths, adverse dropouts, and other serious or potentially serious adverse events

5. Clinical laboratory evaluation

6. Adverse events, including laboratory abnormalities, from sources other than clinical trials

7. Animal data

8. Analysis of dose-response information

9. Drug-drug interactions

10. Drug-demographic and drug-disease interactions

11. Pharmacologic properties other than the property of principal interest

12. Long-term adverse effects

13. Withdrawal effects

I. Drug Abuse and Overdosage (Section II.I)

J. Integrated Summary of Benefits and Risks of the Drug (Section II.J)

STATISTICAL SECTION

A. List of Investigators, List of IND's and NDA's (Section II.A)

B. Background/Overview of Clinical Investigations (Section II.B)

D. Controlled Clinical Studies (Section II.D)

Exactly as shown in the Clinical Section

G. Integrated Summary of Effectiveness Data (Section II.G)

Exactly as reported in the Clinical Section

H. Integrated Summary of Safety Data (Section II.H)

Exactly as reported in the Clinical Section

J. Integrated Summary of Benefits and Risks (Section II.J)

Exactly as reported in the Clinical Section

Appendix A

Examples of Data Presentations

This appendix contains various examples of tabular presentations of data for illustrative purposes. Applicants are encouraged to modify and improve upon these examples or to create better tables for presentation of data.

TABLE 1

Types of Studies and Design Features

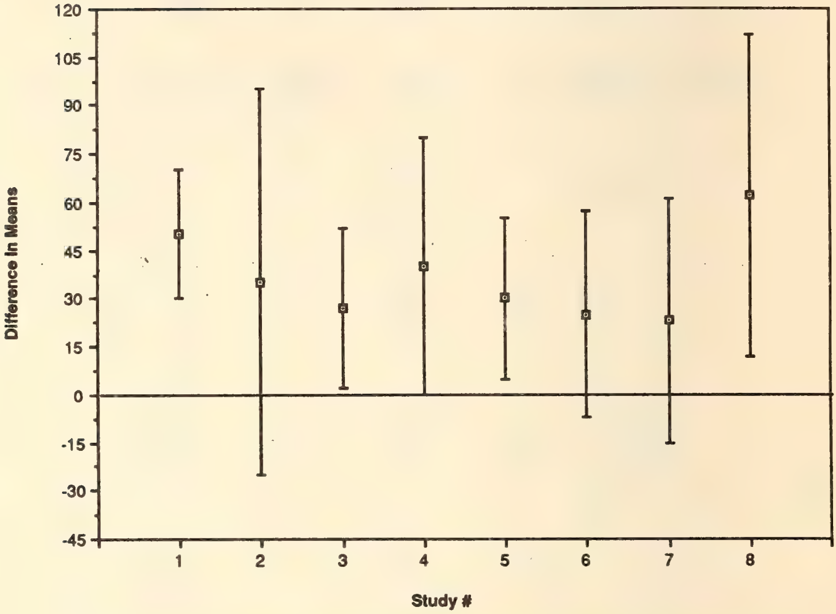
Indication 1 - Hypertension

Protocol #, Investigators, Publications	Completion status (Starting Date)	Location Product code *	Full report Data listings	CRFS	Designs (Blinding, Assignment Parallel vs. X-over (Titra vs. 1st dose)	Treatment, Doses	Number entered each treatment	Age range (Mean)	% M/F B/W/O	Duration of drug treatment
001 Smith, James NEJM 365: 42-48, 1984	Complete (6/5/82)	U.S. A, C	R. Vol.n.k P-1-100 D: Vol.n.1 p 200-400	Vol.n.2,p 355-400 Vol.n.3,p 1-800	DB, randomized parallel,plbo titration	Drug: 20-40mg Placebo b.i.d.	87 42	45-65 (62)	55/45 20/80/0	4 wk
002 Douvier	Complete (6/12/82)	France C	Vol.n.p p 5-86	Vol.n.8, p 1-500 Vol.n.9, p 1-500	DB, randomized X-over, plbo final dose	Drug: 40mg o.d. Placebo Propranolol: 80mg b.i.d.	57 60 55	55-75 (68)	60/40 5/90/5	12 wk
003 Gouo JAMA 48: 82-85, 1985	On-going	GB D, E	Vol.n.q p 4-95	NA	DB, randomized parallel plbo, titra	Drug: 40-80mg o.d. Placebo	125 130	40-60 (58)	50/50 12/60/28	8 wk
004 Jackson	Complete (5/8/81)	U.S. A, C G	Vol.n.r p 1-300	Vol. 12, 1-500 Vol. 13, 1-500 Vol. 14, 1-500	DB, randomized dose-resp., plbo, first dose	Drug.: 20mg o.d. 40mg o.d. 80mg o.d. Placebo	38 40 39 41	65-75 (70)	65/35 30/69/1	2 wk

* A separate list should be provided giving all specific formulations and sizes used and providing a unique code for each.

Figure 1

Difference In Treatment Means* and 95% Confidence Intervals.



*Mean of Test Drug Change From Baseline Minus Mean of Placebo Change From Baseline.

TABLE 2

INTEGRATED SUMMARY OF SAFETY INFORMATION

TOTAL NUMBER (PERCENT) OF DEATHS OR ADVERSE DROPOUTS IN CONTROLLED CLINICAL STUDIES

	TREATMENT GROUP			
	TEST DRUG 162 (100)	CONTROL 163 (100)	P-VALUE	COMMENTS
DEATHS AND ADVERSE DROPOUTS	45 (28)	40 (25)		
DEATHS ACCORDING TO CAUSE				
ACUTE MI				
STROKE				
GI BLEED				
.				
.				
.				
ADVERSE DROPOUTS ACCORDING TO BODY SYSTEM				
DIGESTIVE SYSTEM				
GI PAIN				
DYSPEPSIA				
.				
.				
.				
SKIN AND APPENDAGES				
RASH				
ALOPECIA	63 (39)	7 (4)	0.001	
.				
.				
.				
ETC.				

TABLE 3

INTEGRATED SUMMARY OF SAFETY INFORMATION

FREQUENCY OF A CLINICALLY SERIOUS ADVERSE EVENT BY TIME OF OCCURRENCE FOR ALL SUBJECTS STUDIED (ILLUSTRATION)

TIME INTERVAL OF OCCURRENCE (MONTH)	TEST			CONTROL		
	#EXPOSED	CUMULATIVE #EVENT	RATE	#EXPOSED	CUMULATIVE #EVENT	RATE
0-1						
1-2						
2-3						
3-4						
4-5						
5-6						
CRUDE RATE						

TABLE 4

INTEGRATED SUMMARY OF SAFETY INFORMATION

FREQUENCY OF A CLINICALLY SERIOUS ADVERSE EVENT BY TIME OF OCCURRENCE FOR STUDIES OF VARIOUS TIME PERIODS (ILLUSTRATION)

DURATION OF STUDY (MONTH)	STUDY #	TIME INTERVAL OF OCCURRENCE (MONTH)	TEST #EXPOSED	TEST CUMULATIVE #EVENT	TEST RATE	CONTROL #EXPOSED	CONTROL CUMULATIVE #EVENT	CONTROL RATE
3	1	0-1						
		1-2						
		2-3						
		CRUDE RATE						
	2	0-1						
		1-2						
		2-3						
		CRUDE RATE						
		.						
	.	.						
		.						
	Combined	0-1						
		1-2						
		2-3						
		CRUDE RATE						
6	5	0-1						
		1-2						
		.						
		.						
		.						
		5-6						
		CRUDE RATE						
.								
.								
.								

FIGURE 2
FLOW CHART OF STUDY
(STUDY #)

	Single Blind								Double-Blind							
									Treatment Period							
	Screening Period				Placebo Period				25 mg C bid 12.5 mg C bid 6.25 mg C bid P bid					Standard Treatment		
									R							
Visit	1	(7d)	2	(7d)	3	(7d)	4	(7d)	5	(7d)	6	(7d)	7	(1d)	(6b)	8
Consent	X															
History	X															
Physical	X												X			
BP/BR	X		X		X		X		X		X		X			
body weight	X		X		X		X		X		X		X			X
Capsule count			X		X		X		X		X		X			X
Concomitant medication			X		X		X		X		X		X			X
Adverse experiences			X		X		X		X		X		X			X
EGG	X												X			
CBC	X								X				X			
Clinical chemistry	X								X				X			
Urinalysis	X								X				X			
Blood level of carvedilol									X				X			
Discharge non-qualified patients	X		X		X		X		X							
Assign patient number									X							
24-hour BP									X				X			

TABLE 5

Power for Various Sample Size Allocations

	Allocation of Patients to 2 Groups		Power to Detect Effect Size d		
I.	Total Sample Size 52	d =	.8	1.00	1.20
	Equal (26,26)		.80	.94	.99
	(17,35)		.75	.91	.98
	(13,39)		.68	.86	.95
II.	Total Sample Size 128	d =	.5	.6	.7
	Equal (64,64)		.80	.92	.98
	(43,85)		.75	.88	.96
	(32,96)		.68	.83	.92
III.	Total Sample Size 500	d =	.2	.3	.4
	Equal (250,250)		.61	.92	.99
	(170,330)		.56	.89	.98
	(125,375)		.44	.78	.97

* d = difference between treatments to be detected divided by standard deviation.

TABLE 6

Increase in Sample Size Needed to Maintain Constant Power

	Total Sample Size Required
I. 80% Power for d = .5	
Equal Allocation	128
(1/3, 2/3) Allocation	144
(1/4, 3/4) Allocation	170
II. 80% Power for d = .8	
Equal Allocation	52
(1/3, 2/3) Allocation	59
(1/4, 3/4) Allocation	69

d = difference between treatments to be detected divided by standard deviation

TABLE 7

STUDY #
(Data Set Identification)

Disposition of Patients

	Number of Patients Completing Each Period of Study				
	Randomized	Treated	Week 1	Week 2	Week 4
Test Drug	#	# (%)			
Active Control					
Placebo	______	______	______	______	______
Total	______	______	______	______	______
Comparability test (p-value)		______	______	______	______

TABLE 8

STUDY #
(Data Set Identification)

Listing of Patients Who Discontinued Study

Inv.:

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason
Test Drug								Adverse reaction . . . Therapy failure

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason
Active Control								

Treatment	Patient#	Sex	Age	Last Visit	Duration	Dose	Concomitant Medication	Reason
Placebo								

(Repeat for other investigators)

TABLE 9

STUDY #
(Data Set Identification)

Listing of Patients and Visits Excluded from Efficacy Analysis

Inv.:

Treatment	Patient#	Sex	Age	Visit Excluded	Reason(s)
Test Drug					

Treatment	Patient#	Sex	Age	Visit Excluded	Reason(s)
Active Control					

Treatment	Patient#	Sex	Age	Visit Excluded	Reason(s)
Placebo					

(Repeat for other investigators)

Reference Tables

Summary:

TABLE 10

STUDY #
(Data Set Identification)

Number of Patients Excluded from Efficacy Analysis

Test Drug N =

	Week			
Reason	1	2	4	8
Total				

Similar tables should be prepared for the other treatment groups.

TABLE 11

INDIVIDUAL PATIENT DATA LISTING

KEY DEMOGRAPHIC VARIABLES, BASELINE CHARACTERISTICS AND SCREENING VARIABLES

			DEMOGRAPHIC VARIABLES						CONCOMITANT MEDICATIONS		BASELINE CHARACTERISTICS		ALL SCREENING VARIABLES		
		PATIENT	V1	V2...	V6	DURATION OF	PRIOR	CONCURRENT			V6...	V9	V10	V11	. . .
INVEST.	TREAT.	ID	Sex	Race	HT	ILLNESS	THERAPY	ILLNESS	BASELINE	DURING STUDY	SDBP	SSBP	Smoking	Disease/State	

TABLE 12

SUMMARY OF RESULTS FOR PROGNOSTIC FACTORS FOR ANALYSIS OF TIME TO TREATMENT FAILURE

PROGNOSTIC FACTOR	Study # 1	Study # 2
	(P-value: from Final Cox Regression Model)	
BASELINE PERFORMANCE STATUS	< .01	< .01
AGE	.02	.29
DISEASE FREE INTERVAL	.08	.48
ADJUVANT CHEMOTHERAPY	.53	.01
RACE	.96	.12
EST. COEFF. FOR TREATMENT, BETA*	-.12	-.27
STANDARD ERROR OF BETA	.12	.13
P-VALUE OF TREATMENT EFFECT	.30	.03
e^{BETA}=ESTIMATED RATIO OF HAZARD RATES (ACTIVE:TEST)*	.89	.76
(95% Confidence Interval)	(.70,1.12)	(.59,.99)

* Adjusted for all prognostic factors whose p-value was < .20 (significance at 0.20 level should not be taken as an FDA policy).

TABLE 13

EFFECT OF PROGNOSTIC FACTORS ON THE COMPARISON OF TREATMENTS BY STUDY BEFORE AND AFTER ADJUSTING FOR PROGNOSTIC FACTORS
(T = Test Drug, A = Active Control)

Efficacy Variable	Study # 1	Study #2
Time to Treatment Failure		
Estimated Hazard Ratio (T:A), Unadjusted	0.90	0.81
(95% Confidence Limits)	(.72,1.14)	(.63,1.04)
p-value	.39	.09
Estimated Hazard Ratio (T:A), Adjusted	0.89	0.76
(95% Confidence Limits)	(.70,1.12)	(.59,.99)
p-value	.30	.03
Factors adjusted for are:	PS,AGE,INT[a]	PS,ADJ,RACE[a]

---

[a] PS = Baseline Performance Status, AGE=Age, INT = Disease Free Interval, ADJ = Adjuvant Chemotherapy, RACE = Race

TABLE 14

ADVERSE EVENT LISTING; STUDY

		DEMOGRAPHIC VARIABLES							Time on						Relation	
Invest.	Patient	Age	Sex	Race	WT	HT	TREATMENT/DOSE at Onset	DATE Onset	Rx at Onset	Adverse Event	Duration of Event	Severity of Event	Actions Taken	Outcome	to Rx	Location CRF
A	005	47	M	W	172	75	Placebo									
	007	32	F	B	165	69	Drug 40mg									
	.															
	.															
	.															
.																
.																
.																

TABLE 15

REFERENCE GUIDE FOR TABLES FOR STUDY

			SOURCE OF REFERENCE					
			Statistical Support Information			Data Listing(s)		
Table #	Volume Page	Table Title	Description	Location Vol	Page	Type	Location Vol	Page
1	21 p. 10	Summary of Acute 24 Hour Blood Pressure	ANOVA Tables	21	p. 200	Raw	99	p. 400
			Interaction Info.	21	p. 300	Computed	21	p. 500
. . .								

Appendix B

Guideline for Submission of Data Requested by FDA's Statistical Reviewers

This appendix provides guidance to drug sponsors on submission of data requested by FDA statistical reviewers for analysis.

APPENDIX B

Guideline for Submission of Data Requested by FDA's Statistical Reviewers

A. Statement of Nonendorsement

The specifications provided in this section are recommendations based on the statistical facilities currently in use within the FDA. References to commercial products herein should not be interpreted as an official FDA endorsement.

B. Requirements for Statistical Data Base in Computer Readable Forms

1 Definition and General Structure of a Statistical Data Base

- o The dataset or data base requested for review of each controlled clinical trial reported in the statistical section of a submission will normally be a patient-by-variable type data file.
- o This type of data file is often called a flat file which is simply a two-dimensional array or table of data elements (Table B-1). Each horizontal row in the table is referred to as a case or patient record that contains evaluative information on the patient. Each separate item of information in a patient record is called a field or variable.
- o In practice, the data submitted in a statistical appendix can, and usually should, be subsumed under the following six categories: demographic, efficacy, safety (also side-effects), clinical laboratory, and other or mixed type if only a few variables are being studied.
- o For each of these data categories the patient ID or number should be the first row entry value. The patient number will serve as the key field to merge data from two or more files to form a new "working" file that will consist of a new, combined set of variables. The patient number should be followed sequentially in the row by the appropriate variables in the particular category.

2 For Data on Floppy Diskettes

- o In general, the submittal of these data on diskettes is encouraged if all statistically related files for a given study can be stored on fewer than 10 to 12 double or high density diskettes. The diskettes used should be IBM PC usable, 5.25 inch, and two-sided, IBM PS/2 usable, 3.5 inch, high density, 1.44 MB, or should meet other specifications agreed to by the reviewer and sponsor (e.g., MacIntosh usable).

- The diskettes submitted to the FDA should be properly labeled with the drug sponsor's name, address, and the NDA number or other appropriate reference number.

- The data can be submitted either in the ASCII, flat file format or as SAS datasets.

3 For Data on Magnetic Tapes

- As of the time of publication of this guideline, the standard recording mode for the library tapes used at the FDA Computer Center is 9 track, 6250 bpi. Other options are the 800, 1600, or 38000 (i.e., for 3480 cartridges) bpi. The character set should be either IBM-EBCDIC or ASCII.

- Foreign (non-IBM system generated) tapes should be IBM compatible with no label (i.e., with no headers, just data and tape mark); these foreign tapes should be submitted with the following information for each dataset in a cover letter: dataset name (DSN), volume number (VOL=SER), blocksize (BLKSIZE), record length (LRECL), and record format (RECFM).

- Additional information which will expedite processing of both the foreign and the IBM tapes includes: the type of computer on which data were generated; the type of program, routine, or language used to create the dataset(s); and tape label on the outside of the tape indicating the firm's name, address, and the NDA or some appropriate submittal type reference number.

- The FDA Computer Center normally uses only IBM standard labeled tapes. Although other mode or format may be acceptable, it is recommended that tapes be submitted in a manner consistent with the FDA standards.

- For submission of data on tapes, the sponsor is requested to consult the biostatistical reviewer for specifications relating to the proper submittal of tapes.

4 Specifics and Format of Data

- For all data files contained on floppy diskettes or magnetic tapes, each file should contain not more than 100 variables, and character fields should be minimized. Also, an asterisk (*) should be used for missing values if the file is in ASCII. (SAS uses a dot for missing values.)

- If data are to be submitted in the ASCII, flat file format, the following convention shall be used. The contents of the character fields should not be in quotes. Numeric values should not be expressed as exponentials. Decimal points, if any, should be in fixed columns. Dates should be given as mm/dd/yy. The records should be of uniform length not exceeding 400 characters and/or spaces; the preferred record length is 132 columns or fewer. The fields within each record should be of fixed length with a space between each pair (Tables B-1 and B-2). The first case should be at the first line of the file, with the first allowable character of the first data field being at the first column of the patient record. In addition, there should be a separate data layout file describing each data file submitted.

- For ASCII files the layout should include a list of the field names used, followed by a blank line or record, and then the basic information on each variable in the file: the location and type of variable used and, if appropriate, its permissible range of values (Table B-2).

- For SAS data files, an output of the PROC CONTENTS should be submitted in lieu of the data layout.

- For submission of data on tapes, a printed dump of the first 100 records should be provided. A printed copy of the entire file is highly desirable. In addition, there should be a hard copy of the data layout describing the cases under review.

- In all cases, the data layout should also include the name, address, and telephone number of the contact person and, if practical, of the computer person who prepared the data.

- Frequently the programs, routines, or procedures (including output) used by the drug sponsor on the requested or related data will be helpful and hence should also be submitted.

C. Provision of Consistent File Names

It is anticipated that, with the publication of this guideline, future data files will be submitted to FDA in a computer-readable form. For identification purposes, it is highly desirable that the name for each of the requested data files be consistent with the NDA number or similar reference number. If applicable, this file name should be provided in parentheses immediately after the table(s), figure(s), or result(s) referenced in the submission. In addition, the NDA or similar submission should contain an index table or summary list which cross-references the contents of the files used to their file names. This index table or summary list should contain at least the following basic items: file name, description of file, name of parent file (if any), and related programs/output files (Table B-3). Such provision will not only facilitate the processing of requests for the data, but will also enable FDA's statistical review staff to archive and retrieve the data files in an efficient manner.

The (user specified) data file name should be in the form of "dcrnnnnn.xxx", where "d" denotes FDA's medical review division under which the submission is being evaluated, "c" the type of file to be submitted, and "rnnnnn" the one-character code representing the type of reference number used plus the five-digit reference number. The extension "xxx" is reserved for use by the drug sponsor to indicate sequential protocol and file numbers. These file extensions should be consistent with some chronological ordering scheme; for example, the drug sponsor may use A01 through A50 for program or data files written for, or derived from, the first clinical trial referenced in the submission, A51 through B50 for files related to the second protocol, and so forth. (Note: for files to be submitted on tapes, there are additional required fields and characters which must be specified in accordance with FDA's dataset naming standards.)

For FDA's medical review division (denoted by d above), the following coding scheme should be used:

A = anti-infective drug products
C = cardio-renal drug products
G = gastrointestinal and coagulation drug products
M = metabolism and endocrine drug products
N = neuropharmacological drug products
O = oncology and radiopharmaceutical drug products
S = surgical-dental drug products
V = anti-viral drug products
Z = other or uncertain classification.

The codes for the type of file to be submitted (denoted by c above) are as follows:

P = programs, routines, or procedures
R = results (output) from above programs
H = data layout to be generated in hard copy
D = demographic data
E = efficacy data
S = safety data
C = clinical data in general
L = laboratory data in general
Z = other or mixed type

The one-character code for the type of reference number used (denoted by r above) should be as follows: N for NDA, I for IND, P for PLA, and Z for other. If Z is to be used, then the first five characters of the drug name may be used in case a five-digit reference number (denoted by nnnnn above) is not available; for a drug name that is shorter than five characters, fill in the space with the letter Z at the end.

If for some reason the reference number used is fewer than five digits, fill in the space with leading zero(s).

TABLE B-1

SAMPLE STRUCTURE OF A FLAT FILE CONTAINING PRIMARILY EFFICACY DATA

```
[beginning of file]
patient001 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient002 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient003 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient004 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient005 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient006 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient007 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient008 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient009 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient010 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient011 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient012 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient013 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient014 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient015 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient016 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient017 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient018 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient019 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient020 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
.
.
.
patient998 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
patient999 center# age sex efficacy01 efficacy02 efficacy03 efficacy04 efficacy05 efficacy06 efficacy07 efficacy08 ...
[end of file]
```

TABLE B-2

SAMPLE LAYOUT DESCRIBING VARIABLES IN DATA FILE DCRNNNNN.XXX

Column	Variable	Units	Scale	Description of Comments
1-5	CASENO	none	nominal	case numbered sequentially; key field
6-6				
7-11	ID	none	nominal	patient id (re permanent file)
12-12				
13-14	AGE	year	ratio	age at last birthday in 1987
15-15				
16-16	MDCODE	none	nominal	examining M.D. coded from 1 to 8
17-17				
18-20	SYS77	mm Hg	ratio	systolic blood pressure in 1977, recorded to nearest integer; range: 74 - 143
21-21				
22-24	DIA77	mm Hg	ratio	diastolic blood pressure in 1977, recorded to nearest integer; range: 48 - 98
25-25				
26-28	WT77	lb.	ratio	weight in 1987 to nearest pound; range: 92 - 217
29-29				
30-31	HT77	in.	ratio	height in 1987 to nearest inch; range: 57 - 76
32-32				
33-33	SES	none	ordinal	socio-economic status; 1=high, 5=low
.				
.				
.				
70-71	YRDEATH	none	interval	year of death up to 1987; 00=alive, otherwise year of death recorded

Note: Above data file is of the mixed type.

TABLE B-3

SAMPLE INDEX TO TABLES, DATA, AND ANALYSIS FILES FOR NDA STATISTICAL REPORTS

Drug: Test Drug Indication: Condition X Sponsor: Company A

NDA #: nnnnn Date of Submission: 08/15/87

Study: Protocol # 1

Review Division: Cardio-Renal (110) Code: C

REPORT						DATA FILE				PROCEDURE/PROGRAM FILE				OUTPUT FILE		
Statistical			Clinical			Location				Location				Location		
Vol.	Tab.	Page	Vol.	Tab.	Page	Vol.	Page	Type	Ext.	Vol.	Page	Description	Ext.	Vol.	Page	Ext.
6	1	(3123)	5	3	(2921)	7	(3241+)	E	A16	NL	(3408)	SAS (Means)	A01	8	(3561)	A02
6	2	(3124)	5	1	(2918)	7	(3249+)	S	A05	NL	(3409)	SAS (Means)	A04	8	(3578+)	A06
6	3	(3127)	5	2	(2922)	7	(3252+)	E	A43	7	(3407)	SAS (ANOVA)	A18	8	(3555+)	A11
6	3	"	5	2	"	7	"	E	A43	NL	(3411)	SAS (GLM)	A34	8	(3586+)	A22
6	4	(3143)	5	4	(2927)	7	(3264+)	D	A62	7	(3422+)	GENCAT	A19	8	(3592+)	A37
6	5	(3147)	5	7	(2936)	NL	...	C	A97	NL	...	SAS (GLM)	A63	8	(3613+)	A49
.	.	...	.	.	...	.	...	.	...	..	...	...	...	.	...	...
.	.	...	.	.	...	.	...	.	...	..	...	...	...	.	...	...

Notes: "+" -- More than one page.

NL -- No listing provided in NDA submittal.

Data Files (Type): P = Programs, routines or procedures; R = Results (output); H = Data layout; D = Demographic data; E = Efficacy data; S = Safety data; C = Clinical data; L = Laboratory data; and Z = Others or mixed type.

File Names -- Review division/type/reference number type/reference number . extension; Review division, ref. no. type and reference number are common to all files for a given submittal. The extension number is assigned by the sponsor to describe each file.

Example: CENnnnnn.A16 (efficacy data on pp. 3241+ under Section A)

Page___ of ___

Appendix C

Protocol and Protocol Cover Sheet

As indicated in Section III.B.6 of this guideline, the actual protocol of an individual study should be included as an appendix to the study report, because the FDA clinical and statistical reviewers must have the protocol in order to be able to commence the review of a given study.

A sound protocol is a prerequisite to a successful and well-conducted study. In this appendix, the essential features of a good protocol are described, especially for the benefit of small drug sponsors. Furthermore, for the purpose of expediting the review of a study, it would be very useful for the sponsor to prepare a protocol cover sheet that summarizes the basic features of the given study as proposed in the protocol. An example of a protocol cover sheet is provided in this appendix. Such a protocol cover sheet should enable the reviewers to quickly grasp the principal features of a given study design in relation to the study objective.

APPENDIX C

Protocol and Protocol Cover Sheet

The study protocol for a controlled clinical study

The protocol is a critical document in the evaluation of a study, shaping both the conduct of the trial and the ultimate analyses. It sets out the objectives of the study in clinical terms and then relates these objectives to the statistical hypotheses that are tested. It describes critical features of the study's design and execution such as the experimental design (single-investigator or multi-investigator; parallel or crossover), patient selection and exclusion criteria, the choice of control group(s), the method for treatment allocation, the level and method of blinding, the sample size, the efficacy and safety variables to be measured, any planned interim analyses of the data, the procedures for early termination of the study (if any), the roles and responsibilities of any data-monitoring board, the proposed statistical methods, and the protocol cover sheet. In defining, ahead of time, specific subgroups for separate analysis, and the particular variables that are considered primary end-points, the protocol defines, and limits, the hypotheses the study is able to test.

A well-designed protocol usually will contain the following items. If, for a given study, any of these elements were not incorporated into the protocol used for the study, they should be supplied together with any available supporting data in the application showing that the study was in fact performed as stated.

1. A statement of the specific objectives. In addition to the primary objective, any secondary questions and subgroup hypotheses should be stated explicitly.

2. A clear statement of the study population and all patient selection (inclusion-exclusion) criteria. These criteria should provide assurance that the patients are suitable for the purposes of the study. Thus, the diagnostic criteria for the condition to be treated or diagnosed should be presented as well as any specific requirements for entry (e.g., disease of particular severity, results of specific laboratory tests, physical findings, or particular features of clinical history, such as failure or success on prior therapy).

3. A statement of the basic experimental design. This should describe any initial baseline periods, the treatments to be compared, the study configuration (parallel, crossover, etc.), and the duration of each treatment period. There should be an explanation of the design's suitability for the experimental drug and indication under study. For example, for a crossover design the protocol should consider the likelihood of spontaneous changes in the disease and the need for a reestablishment of baseline between treatment periods.

4. A description of the control group(s). Generally, the accepted types of comparison groups are placebo concurrent control, no treatment concurrent control, active treatment concurrent control, dose comparison concurrent control, and historical control. These are described more fully in the revised NDA regulations at 21 CFR 314.126.

5. A description of the kind of blinding (double-blind, single-blind, etc.) and the specific procedures followed to carry it out (how bottles are labeled, double-dummy techniques, etc.). There should be a discussion of whether the level of blinding chosen is sufficient to minimize bias on the part of patients, observers, and analysts. The protocol should indicate under what circumstances the blinding will be broken.

6. A description of the method of assigning patients to the treatment groups. The method is usually intended to guard against systematic selection bias in the assignment of treatment and to help ensure comparability of the groups with respect to pertinent variables. Bias can be minimized from anticipated sources of variation (such as age, sex, severity of disease, duration of disease, use of drugs or therapy other than the test drug, concomitant illnesses, frequency of observation, etc.) as well as unanticipated sources by randomizing assignments or, if needed and appropriate, using stratified randomization.

7. A description of the efficacy and safety variables to be recorded, the times when they will be recorded, and the methods for measuring them. The appropriateness of the variables and methods should be considered. The methods should generally include those considered by experts to be reliable and accurate. There should be a clear statement as to when measurements are to be made in terms of particular follow-up times and, where appropriate, in relation to the timing of drug administration.

   For trials with multiple efficacy variables the protocol should discuss the planned interpretation of results including appropriate statistical adjustments for multiple testing, if applicable.

   This may involve:

   a. A designation of primary efficacy variables; or

   b. A designated pattern of significant findings among efficacy variables.

Note: If efficacy or safety is to be assessed in terms of categorical ratings, numerical scores, etc., well-defined criteria should be stated to ensure obtaining fairly consistent results among observers. Here the drug sponsor should utilize a method or rating instrument previously shown to discriminate between known effective and ineffective agents.

8. A brief but adequate description of any steps taken to ensure accurate, consistent, and reliable data (e.g., training sessions, instruction manuals, data verification, cross-checking or audits based on probability sampling methods).

9. A description of any planned interim analyses of the data, including the monitoring procedures, the variables to be analyzed, the statistical analyses to be used, including the choice of significance level for each interim analysis, and the frequency of analysis.

10. A description of the circumstances under which the study would be terminated before the planned number of patients has been entered in the study and of circumstances in which individual patients would discontinue the study medication prior to planned completion.

11. A description of the statistical methods to be applied to the data. Here specific questions that the statistical analyses will address in support of the study objectives are identified. For example, a description of the methodology that would be used to incorporate the responses of non-completers would be important. The major end-points for analysis should be identified. If there are several, the means of interpreting inconsistent results and multiple comparisons should be identified. Any subgroups of patients in the trial for whom results will be examined separately should be pre-specified in the protocol. Global efficacy criteria (e.g., sum of symptom-severity scores) or cut-points for defining response that will be used in the analysis to collapse or categorize one or more measured response variables (e.g., "marked" improvement) should be clearly defined.

12. A description of the statistical considerations which were used to determine the number of patients in the study. For example, an analysis of variance table depicting sources of variation and degrees of freedom corresponding to the chosen experimental design is often helpful in clarifying the analytical procedures to be followed and in determining adequate sample sizes for the study.

Protocol Cover Sheet

In order to expedite the review of a study it would be helpful if the drug sponsor provided basic information regarding the essential features of the study protocol in a protocol cover sheet. An example of a protocol cover sheet is given on the following page. Such a cover sheet would enable the reviewer to understand quickly the principal features of a study design in the course of preparing FDA clinical and statistical reviews of an NDA.

PROPOSED PROTOCOL COVER SHEET

Study Phase: II III

Name of Drug:

Active Ingredients:

Study Dosage: Route of Administration: ______________

Objective:

Patient Population:

Structure: Parallel Group Duration of treatment period:

Crossover: # of treatments: # of sequences:
# of periods: Duration of periods:
Washout Between Periods: Yes No

Other: Specify:

Multicenter: Yes No # of centers: Common Training: Yes No

Blinding: None Single-Blind Double-Blind

Method of Patient Assignment: (Randomization: Yes No)
Brief Description:

Concurrent Control: None Placebo No Treatment

Active (specify)

Other dose(s) of test drug (specify)

Estimated Total Sample Size: Statistical rationale provided: Yes No

Primary Efficacy Variable(s):

Adverse Reactions: Volunteered Elicited Both

Plan for data analysis: (proposed statistical methods, interim analyses, etc.)
Yes No

Exh. 8

SPECIAL ARTICLE

JAGS 36:142–149, 1988

Prescribing for the Elderly

Part I: Sensitivity of the Elderly to Adverse Drug Reactions*

Lisa Nolan, BS (Pharm), MS, and Kevin O'Malley, MD, PhD

It has been stated that adverse drug reactions are the inevitable price we pay for the benefits of modern drug therapy.[1,2] Certainly, adverse drug reactions are costly both in terms of the human illness caused and in economic terms.[3,4] Furthermore, iatrogenic disease can undermine the doctor–patient relationship.[5]

The problem of adverse reactions is particularly pertinent to elderly patients because they consume a disproportionate amount of drugs. While those over 65 years of age comprise only 11.7% of the population in the United States, 31% of all drugs are prescribed for this age group.[6] Similarly, in the United Kingdom the elderly are dispensed twice as many prescriptions as the national average.[7] Moreover, alterations in pharmacodynamics and pharmacokinetics with advancing age may alter the response, both wanted and unwanted.[8,9] We have reviewed the evidence for a relationship between chronological age and adverse drug reactions and have attempted to evaluate the contribution of related factors, such as multiple drug therapy and increased morbidity.

THE EPIDEMIOLOGY OF ADVERSE DRUG REACTIONS IN THE ELDERLY

The evidence for an increase in the incidence of adverse drug reactions with increasing patient age is by no means definitive. While some investigators have found a positive correlation between patient age and the incidence of adverse effects,[10–17] many more have failed to demonstrate this relationship.[18–25] Discrepancies are due in part to differences in the populations under study, in the methods of detecting unwanted effects and in the definition of an adverse reaction.

Inpatient Studies Most research has focussed on adverse drug reactions among hospital inpatients (see Table 1). In the early 1960s, Seidl et al[10] in the United States were the first to report that the incidence of adverse reactions among hospital inpatients increased with patient age. Since then investigators in the United Kingdom,[11] Switzerland,[13] and New Zealand[12] have documented a similar increase (see Figure 1). On the basis of these reports elderly patients are two to three times more likely to experience an adverse drug reaction than patients aged 20 to 30 years. Hurwitz[11] reports a sevenfold increase from 3% of patients aged 20 to 30 years to 21% in patients aged 60 to 70 years. On the other hand, studies in the United States,[22,26] Canada[19,21] and India[23] have found no difference in the mean age of patients experiencing a reaction when compared to nonreactors and conclude that patient age is not an important risk factor for adverse drug effects. There is even some evidence that the incidence is reduced in patients over 70 years of age.[11,13,14] This may be due to greater caution in the treatment of very old patients or to difficulties in distinguishing drug-induced problems from events associated with the multiple pathology which is very common in older people and sometimes mistaken for drug-related events.

Estimates of the percentage of patients who experience an adverse drug reaction during hospitalization range from 1.5% to 44% (see Table 1). Because of this range of values it is difficult to estimate accurately the incidence of adverse effects among elderly patients. Smidt and McQueen,[12] in a study of over 9,000 patients, found an incidence as low as 5.6% in patients over 60 years of age. Unlike other investigations, this study was

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0002-8614/88/$3.50

TABLE 1. HOSPITAL INPATIENT STUDIES OF ADVERSE DRUG REACTIONS (ADR)

Investigators	Year	Country	No. of hospitals	Type of wards	Sample size	% Patients with adverse reaction	Effect of age on incidence of ADR	See reference
Seidl et al	1966	USA	1	medical	714	13.6	increase	10
Hurwitz	1969	UK	1	medical, surgical, psychiatric, dermatological	1160	10.2	increase	11
Levy et al	1977	Israel	4	medical	2771	14.5	increase	14
Smidt and McQueen	1972	New Zealand	1	all wards	9104	3.0	increase	12
Klein et al	1976	Switzerland	1	medical	914	18.7	increase	13
Bergman	1971	USA	1	medical	113	21.2	no effect	20
Bennett and Lipman	1977	USA	1	medical, surgical	152	7.2–18.4	no effect	18
Schimmel	1964	USA	1	medical	1014	10.0	no effect	26
Smith et al	1966	USA	1	medical	900	10.8	no effect	22
Ogilvie and Ruedy	1967	Canada	1	medical	731	18.0	no effect	21
Hoddinott et al	1967	Canada	1	medical	104	25.0	no effect	19
Vakil et al	1975	India	–	medical	338	19.8	no effect	23
Cluff et al	1965	USA	1	medical	714	13.6	not evaluated	27
Sidel et al	1967	USA	1	all wards	267	11.3	not evaluated	28
Slone et al	1969	USA	3	medical	2514	30.9	not evlauated	29
Gardner and Watson	1970	USA	1	medical	939	14.6	not evaluated	30
May et al	1977	USA	1	medical	10518	13.0	not evaluated	32
George	1980	UK	1	medical	250	2.4	not evaluated	33
Steel et al	1981	USA	1	medical	815	–	uncertain	34
Wang and Terry	1971	Canada	1	all wards	8991	1.5	not evaluated	35
Gray et al	1973	USA	1	medical	170	43.5	not evaluated	31

not confined to medical services but included patients dmitted to surgical, obstetric, geriatric, orthopedic, psychiatric and pediatric wards. Since medical patients are generally sicker than other patients and exposed to more intensive drug treatment, studies confined to medical wards give an overestimate of the risk of adverse drug reactions in general.[12] Nevertheless, data from such studies are frequently and unwisely used to estimate the cost of adverse drug reactions both in financial terms and in terms of morbidity and mortality.[1,3] Extrapolation to the general hospital population should be made with great caution, if at all, and these data certainly should not be used to estimate risk in ambulatory patients.

Outpatient Studies Although their relevance to everyday medical practice is greater, studies on adverse drug reactions among nonhospitalized patients are scarce, and few address the question of patient age as a determinant of drug toxicity (see Table 2).

In a study of consultations in 24 general practices in the United Kingdom, Lumley et al[36] found a steady increase in the percent of consultations involving an adverse drug reaction from 0.6% of consultations for patients 20 years of age or younger to 2.7% in patients over years of age. In a similar, single-practice study 2.5% of consultations were a direct result of iatrogenic illness but the incidence was independent of patient age.[5]

Over 30% of hospital outpatients experience adverse drug reactions.[24,25,37,40] The discrepancy between the high rate of reactions recorded in these studies and data for hospital inpatients is mainly due to poor definition and documentation of adverse drug reactions and to reporting of minor events often disregarded within inpatient studies. On the other hand, the acute effects of drugs on inpatients are monitored so that reactions occurring only after long-term treatment will not be detected. In one outpatient study,[25] the incidence of adverse reactions was independent of patient age. Twenty-five percent of patients over 65 years of age reported side effects, compared with 34% of younger patients. The authors suggest that the slightly lower rate of reactions among the elderly was probably due to an inability on the part of these patients to recognize the adverse effects of drugs and to attribute their manifestations to drug therapy. In a prospective study of patients discharged from acute medical wards in New Zealand, the distribution of adverse reactions in relation to patient age followed a U-shaped curve, the lowest incidence being in the group 40 to 60 years of age.[24] Hutchinson et al[17] found that the overall incidence of adverse effects increased from 2% in patients aged 18 to 24 years to 8% in those 75 years old or older.

Adverse reactions leading to hospitalization have received considerable attention, and it has been consistently estimated that 3% to 8% of hospital admissions are a consequence of adverse drug reactions (see Table 3). Caranosos et al[42] in the United States and Levy et al[46] in Berlin — both studies participating in the Boston Collaborative Drug Surveillance Program — observed an al-

TABLE 2. HOSPITAL OUTPATIENT AND GENERAL PRACTICE STUDIES OF ADVERSE DRUG REACTIONS (ADR)

Investigators	Year	Country	Study design	Sample size	% patients with ADR	Effect of age on % with ADR	See reference
Mulroy	1973	UK	Study of consultations in a single practice due to iatrogenic illness	9,315	2.5 (consultations)	no effect	5
Kellaway and McCrae	1973	New Zealand	Follow-up investigation of patients discharged from acute medical wards	200	31.5	U-shaped curve of ADRs *vs* age	24
Klein et al	1984	USA	Study of patients attending one hospital outpatient clinic	299	30.0	no effect	25
Campbell et al	1978	USA	Study of patients attending outpatient clinics	154,480	2.2 (consultations)	not evaluated	38
Martys	1979	UK	Follow-up investigation of patients prescribed a single drug in one practice	817	41.0	not evaluated	39
Lumley et al	1986	UK	Study of consultations in 24 general practices	36,470	1.7 (consultations)	increase	36
Meleney and Fraser	1969	USA	Study of patients attending one outpatient clinic	749	35.8	not evaluated	37
Stewart and Cluff	1971	USA	Study of patients attending one outpatient clinic	75	50.6	not evaluated	40
Hutchinson et al	1986	Canada	Surveillance of patients attending one outpatient clinic	1,026	5.0	increase	17

most linear increase in the percent of admissions due to adverse drug reactions with patient age. Adverse drug reactions contribute to the need for hospitalization in 10% of geriatric inpatients.[46-48]

While these studies show that a greater proportion of elderly patients are admitted due to adverse drug reactions, one cannot infer that the elderly are, therefore, more susceptible to unwanted effects. This is because the true denominator in these studies is not the total number of patients admitted to hospital but the number of patients in the relevant community exposed to drug treatment. Such studies are best suited to illustrating the economic consequences of iatrogenic disease but do not add to our understanding of factors affecting patient susceptibility to adverse drug reactions.

It is clear that the generally held view of there being an increased rate of adverse drug reactions in the elderly is based on a few studies carried out on hospital inpatients[10,14] and perhaps on anecdotal data and clinical impressions. Much of this assumption is perpetuated as fact in the medical literature, and studies failing to show an age-related increase in unwanted effects are generally disregarded. On the other hand, failure to demonstrate an association between age and adverse drug reactions in epidemiological studies does not rule out an important contribution of age as a determinant of unwanted effects since the use of lower doses or more careful monitoring of drug effects could offset an actual difference in drug sensitivity in the geriatric population. Conversely, a positive correlation between patient age

TABLE 3. HOSPITAL ADMISSIONS DUE TO ADVERSE DRUG REACTIONS (ADR)

Investigators	Year	Country	No. hospitals studied	Type of wards studied	Sample size	% Admitted due to ADR	Effect of age on percent admitted	See reference
Caranosos et al	1974	USA	1	medical	6,063	2.9	increase	42
Hurwitz	1969	UK	1	all wards	1,268	2.9	not evaluated	41
Levy et al	1980	Berlin	1	medical	2,933	5.7	increase	46
Levy et al	1979	Israel	1	medical	2,499	4.1	no effect	45
Miller	1974	multicenter	7	medical	7,017	3.7	not evaluated	43
McKenny and Harrison	1976	USA	1	medical	216	7.9	no effect	44
Cooke et al	1985	South Africa	1	medical	300	4.7	not evaluated	47

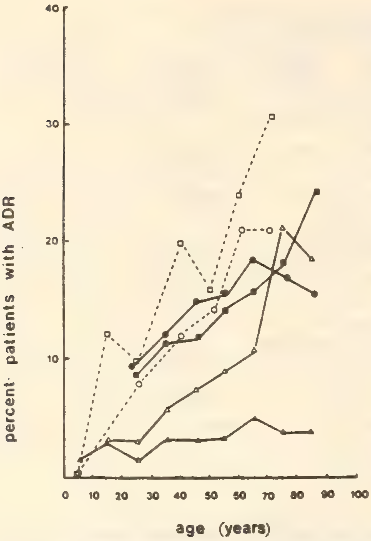

FIGURE 1. *Relationship between the patient age and the incidence of adverse drug reactions. Adapted from Levy et al (●),[14] Klein et al (○ male, □ female),[13] Seidl et al (■),[10] Smith and McQueen (▲),[12] and Hurwitz (△).[11] ADR = adverse drug reactions.*

and the incidence of adverse drug reactions does not necessarily mean that the elderly are more sensitive to the adverse effects of drugs. In examining the influence of patient age, none of the above studies (with one exception[17]) control for other factors which could account for a higher incidence of adverse drug reactions in elderly patients.

FACTORS WHICH INFLUENCE PATIENT SUSCEPTIBILITY TO ADVERSE DRUG REACTIONS

Multiple Drug Therapy It has been consistently shown that the incidence of adverse drug reactions increases with the number of drugs taken.[17-20,22-24,27,31,32,34,49] In hospital inpatient studies, Hurwitz and Wade,[49] Hoddinott et al,[19] and Cluff et al[27] report that patients who experienced an adverse reaction took, on average, twice as many drugs as patients with no reaction (6.3 *vs* 12.5, 4 *vs* 9 and 5.9 *vs* 11.2, respectively). In one study, the severity of adverse reactions was related to the number of drugs taken. Patients with no reactions took a mean of 7.3 drugs; patients with minor reactions a mean of 11.7 drugs; and patients with severe complications took 17.1 drugs.[34] A positive correlation between adverse drug reactions and multiple drug therapy has also been noted among outpatients.[24]

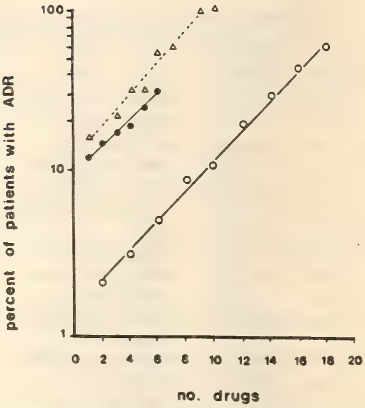

FIGURE 2. *Relationship between the number of drugs taken concurrently and the incidence of adverse reactions. Adapted from Kellaway and McCrae△,[24] Williamson and Chopin ●,[40] and Smith et al ○.[22] ADR = adverse drug reactions.*

The incidence of adverse drug reactions increases exponentially rather than linearly with the number of drugs given tc patients (see Figure 2), indicating that the effects of multiple drug use are not simply additive. A number of factors may contribute to this disproportionate rise. First, high prescribing rates are associated with severity of illness.[22] Patients who take many drugs are more severely ill and perhaps predisposed to adverse effects. Alternatively, symptoms of disease in severely ill patients may be erroneously attributed to drug treatment. Second, drug interactions may play a part. May et al[32] demonstrated that the rates of reactions to individual drugs were dependent upon the number of drugs given concurrently. Finally, the use of drugs to treat adverse reactions, eg, antihistamine for ampicillin rash, will contribute to the strong association between the number of drugs taken during hospitalization and the incidence of unwanted effects.

Of all the factors which influence patient susceptibility to adverse drug reactions, multiple drug therapy has been most strongly and most consistently associated. Elderly patients, particularly those in hospital, are prescribed more drugs than younger patients.[50,51] Thus, any increase in the rate of adverse reactions with advancing age may be a simple consequence of increased exposure to drugs rather than an effect of aging on susceptibility. We are aware of only one study which takes account of the greater frequency of multiple drug use in the elderly. Hutchinson et al[17] expressed their data both as rates of adverse reaction per patient and rates of adverse reaction per drug. They found an age-related increase in the rate per patient but found no correlation between age and rate per drug.

Multiple Disorders and Severity of Disease Pathological conditions can alter drug disposition by increasing steady state concentration or prolonging half-life.[52] Thus, severe morbidity may influence patient susceptibility to adverse drug reactions. Surprisingly, the relationship between adverse reactions and severity of disease has not been studied and (with one exception[34]) investigations do not stratify for disease state when evaluating risk factors. Geriatric patients are more likely to be severely ill when admitted to hospital[34] and this might partly account for any increased incidence of adverse reactions with increasing age. It is possible, particularly in patients who are very ill, that some of the various events related to the illness may be interpreted as being drug-induced. Indeed while Steel et al[34] found a simple association between patient age and the incidence of adverse reactions, no correlation was found when data were corrected for disease severity.

Types of Drugs Prescribed Clearly, some drugs are more likely to cause adverse reactions than others. Unfortunately, drugs most commonly implicated in adverse drug reactions are more often prescribed for elderly patients.

Digoxin, which is used extensively in geriatric patients, is responsible for over 20% of all adverse drug reactions occurring in hospital inpatients[10,13,21] and one third of these reactions are life-threatening.[34] The toxicity of digoxin is enhanced by co-administration of diuretics, a problem particularly pertinent in geriatric medicine.[11] Prescribing rates for other drugs with a low therapeutic index such as anticoagulants, insulin, and antiarrhythmics are also greater among elderly patients.[50,51] Thus, an increased incidence of adverse drug reactions with advancing age may reflect in part the types of drugs prescribed.

Both Smith et al[22] and Cluff et al[27] report a high incidence of unwanted effects with antihypertensive drugs. However, these studies date from the early 1960s when adrenergic neurone-blocking drugs and reserpine were commonly used in the treatment of hypertension.[22] Thus data from earlier studies may have limited relevance to modern medicine. Indeed, Levy et al,[14] in comparing rates of reactions from two periods (1969 to 1972 *vs* 1973 to 1976), report a 60% fall in the incidence of adverse drug reactions and ascribe this to the use of safer drugs in recent years. In a study of adverse reactions leading to death, Irey[53] stressed that the great majority of agents responsible for adverse drug reactions were not new drugs. Eighty-five percent of deaths involved drugs that were in use for over 20 years at the time of the study. It is perhaps ironical that physicians are cautioned against prescribing newer drugs for elderly patients while older and well-tried agents are considered "safe."

Altered Pharmacokinetics Seventy to eighty percent of adverse drug reactions are dose-related.[10,11] Therefore, alterations in drug metabolism,[54,55] renal elimination,[56,57] and distribution[58,59] that result in higher serum and tissue concentrations in the elderly should lead to a higher incidence of adverse drug reactions. It is this line of reasoning that has lead to the assumption that the elderly are more sensitive to drug toxicity.

Many investigations have found that liver disease is not related to the incidence of adverse drug reactions.[11,22,27,45] Thus slight changes in hepatic drug-metabolizing capacity with increasing patient age will have little clinical significance in terms of drug toxicity. Changes in the volume of distribution may be more relevant. All else being equal, an increase in the volume of distribution prolongs plasma elimination half-life and hence the duration of drug action. For example, the half-life of diazepam increases linearly, from 20 hours at 20 years to 90 hours in those over 80 years, because of an increase in the volume of distribution rather than reduced hepatic metabolism.[59] On the other hand, a decline in renal function is associated with a higher incidence of adverse drug reactions.[22,45] Smith et al[22] report that the incidence of adverse reactions rose from 9% in patients with a blood urea nitrogen less than 20 mg/100 mL to 24% in patients with an elevated BUN. Reduced renal function in the elderly may contribute to a higher incidence of adverse effects where drugs are predominantly eliminated by the renal route.

Altered Pharmacodynamics Relatively little attention has been paid to studying the effect of age on pharmacodynamics (the response to a given concentration of drug at the receptor site). In some cases the response is increased[60–63] while in other cases the response is decreased, notably with beta-adrenoceptor–mediated responses.[64–66] Where responsiveness is increased, the elderly may be more sensitive to adverse effects and dosage should be altered accordingly. This sensitivity has been observed particularly with drugs acting on the central nervous system. Cook and colleagues found that the plasma concentrations of diazepam required for sedation fell markedly between the ages of 20 and 80 years.[62] The extent and duration of action of nitrazepam on psychomotor function is more marked in the elderly when compared with younger subjects despite similar plasma concentrations.[63] This increase in sensitivity may account for the observation that adverse reactions to benzodiazepines occur more frequently in elderly patients.[67,68]

Homeostatic mechanisms become less effective as age progresses. Baroreflex activity, for example, has been shown to decline with age.[69] This decline may contribute to the greater risk of postural hypotension in elderly patients taking certain antihypertensives.

LIMITATIONS OF THE DATA AVAILABLE

There are many problems associated with adverse drug reactions–monitoring, and these must be kept in mind when assessing the evidence for an increased incidence of adverse reactions in the elderly. The first problem is the definition of an adverse drug reaction. In an effort to standardize reporting, the World Health Organization in 1969 defined an adverse reaction as "one that is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy." [70] But many reports, even those recently published, do not adhere to this definition, whereas others fail to include any definition.[36,38,40,44] A second difficulty is the assessment of the causal relationship between the event and drug therapy. Adverse drug reactions constitute clinical and laboratory findings which often occur in the absence of drug treatment[71] and furthermore, clinicians frequently disagree on the probability of a link between the event and drug treatment.[72] Recent attempts to improve the classification of adverse drug reactions have been made by the introduction of algorithms which provide detailed operational criteria for ranking the probability of drug causation when an adverse reaction is suspected.[73–75] While algorithms can improve the consensus of opinion between different clinicians,[76] it has been argued that they simply substitute the opinion of the authors of the algorithm for that of clinical assessors.[77] Thus the assessment of adverse drug reactions remains subjective and may contribute to tne disparities between various studies. Ideally, one should have appropriate controls so that the incidence of background events would be taken into account. Placebo-controlled investigations of new drugs provide a controlled means of measuring the incidence of adverse reactions. Because it is now obligatory in many countries to include older patients in these investigations, such studies should help to determine whether adverse drug reactions occur more frequently in older individuals.

No serious attempts have been made to quantify the extent of iatrogenic disease outside hospitals. The data available are very fragmentary. Some progress has been made in recent years with the introduction of national reporting systems. However, reporting rates are low,[36] and these data lack a denominator (all patients exposed to drug treatment).[78] Thus factors affecting patient susceptibility to adverse drug reactions cannot be comprehensively evaluated.

Much of the data available date from the 1960s when there was an awakening of interest in adverse drug reactions as a consequence of the thalidomide disaster. However, the relevance of these data to current medical practice is probably limited. While it is usually assumed that the growth in drug innovation has lead to the introduction of "more potent and more toxic drugs," the data presented here do not support this generalization. It is possible that a greater awareness of the potential for adverse reactions and stricter licensing requirements will contribute to safer drug use and a fall in the incidence of unwanted effects. Also, the publicity given to the problems of drug treatment in the elderly in the past decade should lead to greater caution in the administration of drugs to elderly patients. This might account for a failure to uncover an age-related increase in the incidence of adverse drug reactions in more recent studies.

CONCLUSIONS

Klein et al[79] have drawn attention to the need for a reassessment of the problem of adverse reactions in the elderly. This review of the literature reinforces their conclusions. Remarkably little data is available to support the commonly held view that the incidence of adverse drug reactions increases with patient age. Limited evidence suggests that elderly patients in hospitals are more likely than younger patients to experience an adverse reaction. The incidence of reactions among outpatients, both young and old, is unknown. In the absence of recent, properly controlled, epidemiological studies, covering both institutionalized and community-living patients, we cannot conclusively state that the elderly are or are not more prone to adverse drug reactions. Even is we accept limited evidence that the incidence is greater among elderly patients, we cannot infer that this is due to the biological effects of aging.

Polypharmacy is more consistently associated with adverse drug reactions, and it is likely that severe illness, multiple pathology and the associated high level of prescribing is much more important than age itself. In future studies, control for severity of illness and multiple drug therapy will be imperative if valid statements about the effects of single variables, such as age, are to be made. In practice, the risks of drug toxicity in the elderly, as indeed in all patients, can be minimized by avoidance of unnecessary polypharmacy, by choosing the least toxic drugs where possible, and by careful consideration of the dosage requirements for individual patients. The elderly patient wil not experience an adverse reaction simply because of old age.

REFERENCES

1. Jick H: Drugs—remarkably nontoxic. N Engl J Med 291:824, 1974

2. Barr DP: Hazards of modern diagnosis and therapy—the price we pay. JAMA 129:1452, 1955
3. Melmon K: Preventable drug reactions, causes and cures. N Engl J Med 284:1361, 1971
4. Campbell WH, Johnson RE, Senft RA, et al: Treated adverse effects of drugs in an ambulatory population. Med Care 15:599, 1977
5. Mulroy R: Iatrogenic disease in general practice. Br Med J 2:407, 1973
6. Lamy PP: New dimensions and opportunities. Drug Intell Clin Pharm 19:399, 1985
7. Report of the Royal College of Physicians: Medication for the elderly. J R Coll Physicians Lond 18:7, 1984
8. Bender AD: Drug sensitivity in the elderly, *in* Crooks J, Stevenson IH (eds): Drugs and the elderly. Oxford, The Macmillan Press, 1979, p 147
9. Greenblatt DJ, Sellers EM, Shader RI: Drug disposition in old age. N Engl J Med 306:1081, 1982
10. Seidl CG, Thornton GF, Smith JW, et al: Studies on the epidemiology of adverse drug reactions: III. Reactions in patients on a general medical service. Bull John Hopkins Hosp 119:299, 1966
11. Hurwitz N: Predisposing factors in adverse reactions to drugs. Br Med J 1:536, 1969
12. Smidt WA, McQueen EG: Adverse reactions to drugs: a comprehensive inpatient survey. N Z Med J 76:397, 1972
13. Klein U, Klein M, Sturm H, Rothenbuhler M, et al: The frequency of adverse drug reactions as dependent upon age, sex and duration of hospitalization. Int J Clin Pharmacol 13:187–195, 1976
14. Levy M, Kletter-Hemo D, Nir I, et al: Drug utilization and adverse drug reactions in medical patients. Comparison of two periods 1969–1972 and 1973–1976. Isr J Med Sci 13:1065, 1977
15. Bottiger LE, Furhoff AK, Holmberg L: Drug induced blood dyscrasias. Acta Med Scand 205:457, 1979
16. Bottiger LE, Furhoff AK, Holmberg L: Fatal reactions to drugs. Acta Med Scand 205:451, 1979
17. Hutchinson TA, Flegel KM, Kramer MS, et al: Frequency, severity and risk factors for adverse reactions in adult outpatients: A prospective study. J Chron Dis 39:533, 1986
18. Bennett BS, Lipman AG: Comparative study of prospective surveillance and voluntary reporting in determining the incidence of adverse drug reactions. Am J Hosp Pharm 34:931, 1977
19. Hoddinott BC, Gowdey LW, Coulter WK, et al: Drug reactions and errors in administration on a medical ward. Can Med Assoc J 97:1001, 1967
20. Bergman HG, Aoki VS, Black HJ, et al: A new role for the pharmacist in the detection and evaluation of adverse drug reactions. Am J Hosp Pharm 28:343, 1971
21. Ogilvie RI, Ruedy J: Adverse drug reactions during hospitalisation. Can Med Assoc J 97:1450, 1967
22. Smith JW, Seidl LG, Cluff LE: Studies on the epidemiology of adverse drug reactions. Ann Int Med 65:629, 1966
23. Vakil BJ, Kulkarni RD, Chabria NL, et al: Intense surveillance of adverse drug reactions. J Clin Pharmacol 15:435, 1975
24. Kellaway GSM, McCrae E: Intensive monitoring of adverse drug effects in patients discharged from acute medical wards. N Z Med J 78:525, 1973
25. Klein LE, German PS, Levine DM, et al: Medication problems among outpatients. A study with emphasis on the elderly. Arch Int Med 144:1185, 1984
26. Schimmel EM: The hazards of hospitalization. Ann Int Med 60:100, 1964
27. Cluff LE, Thornton G, Seidl L, et al: Epidemiological study of adverse drug reactions. Trans Assoc Am Physicians 78:255, 1965
28. Sidel VW, Koch-Weser J, Barnett O, et al: Drug utilization and adverse reactions in a general hospital. JAMA 141:80, 1967
29. Slone D, Gaetano LF, Lipironte L, et al: Computer analysis of epidemiological data on effect of drugs on hospital patients. Pub Health Rep 84:39, 1969
30. Gardner P, Watson LJ: Adverse drug reactions: A pharmacist-based monitoring system. Clin Pharmacol Ther 11:802, 1970
31. Gray TK, Adams LL, Fallon HJ: Short-term intense surveillance of adverse drug reactions. J Clin Pharmacol 13:61, 1973
32. May FE, Stewart RB, Cluff LE: Drug interactions and multiple drug administration. Clin Pharmacol Ther 22:322, 1977
33. George CF, Kingscombe PM: Can adverse drug reactions be prevented? Adverse Drug Reactions Bull 80:288, 1980
34. Steel K, Gertman PM, Crescenzi C, et al: Iatrogenic illness on a general medical service at a university hospital. N Eng J Med 304:638, 1981
35. Wang RI, Terry LC: Adverse drug reactions in a Veterans Administration hospital. J Clin Pharmacol 11:14, 1971
36. Lumley LE, Walker SR, Hall CG, et al: The underreporting of adverse drug reactions seen in general practice. Pharmaceut Med 1:205, 1986
37. Meleny HE, Fraser ML et al: A retrospective study of drug usage and adverse drug reactions in hospital outpatients: Final report. Drug Inf Bull 2:124, 1969
38. Campbell WH, Johnson RE, Senft RA, et al: Adverse drug reactions in a disadvantaged population. J Community Health 3:205, 1978
39. Martys CR: Adverse reactions to drugs in general practice. Br Med J 2:1194, 1979
40. Stewart RB, Cluff LE: Studies on the epidemiology of adverse drug reactions: VI. Utilization and interactions of prescription and nonprescription drugs in outpatients. John Hopkins Med J 129:319, 1971
41. Hurwitz N: Admissions to hospitals due to drugs. Br Med J 1:539, 1969
42. Caranosos CJ, Stewart RB, Cluff LE: Drug-induced illness leading to hospitalization. JAMA 228:713, 1974
43. Miller RR: Hospital admissions due to adverse drug reactions. Arch Int Med 134:219, 1974
44. Mc Kenney JM, Harrison WL: Drug-related hospital admissions. Am J Hosp Pharm 33:792, 1976
45. Levy M, Lipshitz W, Eliakim M: Hospital admissions due to adverse drug reactions. Am J Med Sci 227:49, 1979

46. Levy M, Kewitz H, Altwein W, et al: Hospital admissions due to drug reactions: A comparative study from Jerusalem and Berlin. Eur J Clin Pharmacol 17:25, 1980

47. Cooke DI, van der Mevwe W, Pudifin DJ: Hospital admissions for adverse reactions to drugs and deliberate self-poisoning. South Afr Med J 67:770, 1985

48. Williamson J, Chopin JM: Adverse reactions to prescribed drugs in the elderly: A multicentre investigation. Age Ageing 9:73, 1980

49. Hurwitz N, Wade OL: Intensive hospital monitoring of adverse reactions to drugs. Br Med J 1:531, 1969

50. Sotaniemi E, Palva IP: The use of polypharmaceutical drug therapy in a medical ward. Ann Clin Res 4:158, 1972

51. Boethius G: Recording of drug prescriptions in the county of Jamtland, Sweden: Pattern of drug usage in 16600 individuals during 1970–75. Acta Med Scand 202:241, 1977

52. Lamy PP, Lesko LJ: Altered drug action in the elderly in Aller (ed): Annual reports in medicinal chemistry. Academic Press, 1985, p 295

53. Irey NS: Adverse drug reactions and death. A review of 827 cases. JAMA 236:575, 1976

54. Roberts RK, Wilkinson GR, Branch RA, et al: Effect of age and parenchymal liver disease on the disposition and elimination of chlordiazepoxide. Gastroenterology 75:479, 1978

55. Kelly JG, McGarry K, O'Brien E, et al: Bioavailability of labetalol increases with age. Br J Clin Pharmacol 14:304, 1982

56. Cusack B, Horgan J, Kelly JG, et al: Digoxin in the elderly: Pharmacokinetic consequences of old age. Clin Pharmacol Ther 25:772, 1979

57. Redolfi A, Borgogelli E, Ladola E: Blood level of cimetidine in relation to age. Eur J Clin Pharmacol 15:257, 1979

58. Shader RI, Greenblatt DJ, Harmatz JS, et al: Absorption and distribution of chlordiazepoxide in young and elderly male volunteers. J Clin Pharmacol 17:709, 1977

59. Klotz U, Avant GR, Hoyumpa A, et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 55:347, 1975

60. O'Malley K, Stevenson IH, Ward C, et al: Determinants of anticoagulant control in patients receiving warfarin. Br J Clin Pharmacol 4:309, 1977

61. Shepherd AMM, Hewick DS, Moreland TA, et al: Age as a determinant of sensitivity to warfarin. Br J Clin Pharmacol 4:315, 1977

62. Cook PJ, Flanagan R, James IM: Diazepam tolerance: Effect of age, regular sedation and alcohol. Br Med J 289:351, 1984

63. Castleden CM, George CF, Marcer D, et al: Increased sensitivity to nitrazepam in old age. Br Med J 1:10, 1977

64. Vestal RE, Wood AJJ, Shand DG et al: Reduced beta-adrenoceptor sensitivity in the elderly. Clin Pharmacol Ther 26:181, 1979

65. Dillon N, Chung S, Kelly J, et al: Age and beta-adrenoceptor–mediated function. Clin Pharmacol Ther 27:769, 1980

66. Cotter T, O'Malley K: Decreased neutrophil cyclic AMP response to isoprenaline stimulation in the elderly. Clin Sci 65:155, 1983

67. Greenblatt DJ, Allen MD: Toxicity of nitrazepam in the elderly: A report from the Boston Collaborative Drug Surveillance Program. Br J Clin Pharmacol 5:407, 1978

68. Boston Collaborative Drug Surveillance Program: Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. N Engl J Med 288:277, 1973

69. McGarry K, Laher M, Fitzgerald D, et al: Baroreflex function in elderly hypertensives. Hypertension 5:763, 1983

70. World Health Organization: International drug monitoring—the role of the hospital. Drug Intell Clin Pharm 4:101, 1970

71. Reidenberg MM, Lowenthal DT: Adverse nondrug reactions. N Engl J Med 279:678, 1968

72. Koch-Weser J, Sellers EM, Zacest R: The ambiguity of adverse drug reactions. Eur J Clin Pharmacol 11:75, 1977

73. Karch FE, Lasagna L: Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther 21:247, 1977

74. Kramer MS, Leventhal JM, Hutchinson TA, et al: An algorithm for the operational assessment of adverse drug reactions. JAMA 242:623, 1979

75. Venulet J, Ciucci A, Bernecker GC: Standarized assessments of drug–adverse reaction associations—rationale and experience. Int J Clin Pharmacol Ther Toxicol 18:381, 1980

76. Naranjo LA, Busto U, Sellers EM, et al: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239, 1982

77. Girard M: Testing the methods of assessment for adverse drug reactions. Adverse Drug React Acute Poisoning Rev 4:237, 1984

78. Moussa MAA, Bayoumi A, Al-Khars AA, et al: Adverse drug reaction monitoring in Kuwait (1981–1984). J Clin Pharmacol 25:176, 1985

79. Klein LE, German PS, Levine DM: Adverse drug reactions among the elderly: A reassessment. J Am Geriatr Soc 29:525, 1981

STATUS REPORT

ON

PATIENT EDUCATION ACTIVITIES
(1983-1988)

FOOD AND DRUG ADMINISTRATION
OFFICE OF CONSUMER AFFAIRS
ROCKVILLE, MD

1988

Prescription Drug, Medical Device, and X Ray Patient Education Activities

OVERVIEW

To ensure that prescription drugs and medical devices are used properly, FDA coordinates the development and implementation of major patient education initiatives in the public and private sectors. Since the early 1980s, FDA has placed emphasis on patient education programs for prescription drugs and x rays. Activities were also conducted with women's health care devices and hearing aids. These initiatives have been concentrated in three main areas: urging patients to request information; encouraging health professionals to provide information; and monitoring patient education activities.

The prescription drug initiatives began in 1982 with the formation of the National Council on Patient Information and Education (NCPIE). The results of an FDA survey completed that year indicated that most patients were not given sufficient information when they received a prescription.

In 1983 FDA and NCPIE launched the Get the Answers campaign urging patients to ask their health professionals questions about their prescriptions. The "Get the Answers" message was widely disseminated to consumers and health professional organizations through news releases, advice columns, and multiplier groups. FDA also worked with the Social Security Administration to disseminate the "Get the Answers" message to 36 million social security recipients. In 1983 several private sector organizations (the American Medical Association, the U.S. Pharmacopeia, and the American Association of Retired Persons) developed patient drug leaflet systems for health professionals to use with their patients.

In 1984 FDA conducted a successful Ask the Doctor About Prescription Drugs Day in cooperation with the American Academy of Family Physicians and Call for Action. FDA received the National Association of Consumer Agency Administrator's 1985 Best Program Award for this initiative which was conducted in cities across the country. Also in 1984, NCPIE and FDA launched a Give the Answers campaign to encourage health professionals to utilize the drug information systems that were available.

In 1985 FDA and other organizations targeted prescription drug patient education efforts to two major groups: the elderly, who take more drugs per capita than do younger individuals in proportion to their representation in the population; and Hispanics, who are often unreached by English language campaigns. Also, NCPIE launched the Work Site Initiative which is designed to encourage corporations to disseminate the Get the Answers campaign materials to their employees and customers.

In 1986 FDA participated in the first national Talk About Prescriptions Month sponsored by NCPIE. The second annual Talk About Prescriptions Month campaign was conducted during October 1987. Also during 1987 there was increased participation by business, health organizations, and state and local governments in patient education activities.

In 1987 NCPIE announced a public education campaign to improve communications between health professionals and the elderly. The campaign consists of a 30-second TV PSA, a 30-second radio PSA, a color brochure, and print ads for consumer and professional publications.

In 1988 the public education campaign, Before You Take It Talk About It, got underway. Also, the District of Columbia Senior Citizen Medication Education Program was launched; the program will reach every elderly resident's home by mid-1989. And FDA again participated in the NCPIE-sponsored Talk About Prescriptions Month.

The Agency is also continuing its nationwide diagnostic x-ray public information campaign which began in 1980. The goal of the campaign is to stimulate consumers to take an active role in their health care to ensure that they receive the maximum benefit with the minimum risk of diagnostic x rays. Over the years, FDA has initiated campaigns in the areas of mammography, intrauterine contraceptive devices, toxic shock syndrome, home-use diagnostic devices, and indoor tanning devices.

Virtually all FDA offices and staffs have conducted activities in support of FDA's and NCPIE's patient education initiative. A list of contact people appears at the end of the status report.

PRESCRIPTION DRUG INITIATIVES

I. Urging Patients to Request Information

The Get the Answers campaign is the primary education program urging patients to ask their health professionals questions about their prescription drugs. FDA, NCPIE, and various other organizations initiated this public communications effort in July 1983. The major component of the campaign is a medical data wallet card that lists the five questions patients should ask when they get a prescription:

1. What is the name of the drug and what is it supposed to do?

2. How and when do I take it -- and for how long?

3. What foods, drinks, other medicines, or activities should I avoid while taking this drug?

4. Are there any side effects, and what do I do if they occur?

5. Is there any written information available about the drug?

FDA, NCPIE, and many other organizations helped disseminate the "Get the Answers" message to millions of consumers. For example, FDA worked with the Social Security Administration, the Veterans Administration, and the Consumer Information Center to offer FDA materials on the proper use of medication to over 40 million consumers whom these organizations contact each year.

FDA has also targeted the "Get the Answers" message to specific populations, such as Hispanics and the elderly. There are over 15 million Hispanic consumers in the continental United States. Due to language and cultural differences, a large portion of this population may not be reached by traditional patient education messages.

In order to reach Hispanics, FDA has conducted the following initiatives: worked with the National Coalition of Hispanic Health and Human Services Organizations (COSSMHO) to translate the medical data wallet card into Spanish; joined with groups such as the National Hispanic Council on Aging to distribute these cards to Spanish-speaking consumers; presented three conferences to promote interest and support for incorporating patient education into Puerto Rico's public and private school curricula; and worked with groups such as the Latin Chamber of Commerce to develop and coordinate an Hispanic patient education program in Florida.

In addition to continuation of the Get the Answers campaign, several new initiatives were conducted to encourage patients to request information about their prescriptions. These initiatives are described below.

II. Talk About Prescriptions Month

In 1986 NCPIE and FDA initiated the first national Talk About Prescriptions Month. The purpose of the month was to stimulate activity to motivate health professionals to give, and consumers to seek, the information needed for safe and effective medication use. DHHS Assistant Secretary for Health Robert Windom and FDA Commissioner Frank Young joined NCPIE Chairman Paul Rogers at the NCPIE press conference on October 2, 1986, to announce the campaign. NCPIE developed and distributed a campaign newspaper, designed as a do-it-yourself kit, containing available materials/resources to support activities planned during October.

Based on the success of the first Talk About Prescriptions Month, NCPIE decided to make it an annual event. During October 1987, the second Talk About Prescriptions Month emphasized the problem of improper medication use among the elderly. Once again, FDA and NCPIE held a press conference to: kick off the month;

release the NCPIE report on improper medication use among older people; and announce a public education campaign on improving communications between health professionals and the elderly.

The theme of Talk About Prescriptions Month 1988 was "Prescriptions: Communicate Before You Medicate." The campaign focused on children and safe use of medicines. A report based on a National Library of Medicine literature search of children and medicine is in preparation and a press conference will be held in 1989 to announce the campaign and availability of the report.

FDA distributed the Talk About Prescription Month campaign newspaper to newsletter editors, health professional organizations, and several thousand consumers and multiplier organizations. FDA urged these groups to sponsor activities in support of the month; many indicated that they would conduct special programs and classes, give speeches, prepare press releases, Public Service Announcements (PSAs) or telephone tapes, or distribute posters and brochures. In addition, the governors from several states signed proclamations to honor national Talk About Prescriptions Month. Articles promoting the month were included in the October 1988 *FDA Consumer, Pharmacy Times*, and numerous other publications.

As a result of Talk About Prescriptions Month, the District of Columbia launched a Senior Citizen Medication Education Program at a press conference in October 1988 featuring FDA Deputy Commissioner James Benson, D. C. Mayor Marion Barry, and D. C. Health Commissioner Reed Tuckson. Eighty-five thousand of NCPIE's *Before You Take It, Talk About It* brochures have been printed and will be mailed to every senior resident's household.

III. Media Campaign

In 1987 NCPIE announced its public education campaign, which consisted of a 30-second TV PSA, a 30-second radio PSA, a four-color brochure, and print ads for consumer and professional publications. The campaign focused on the need to improve basic communication about prescription medicines between older patients and their health care professionals as emphasized in the campaign theme, "Before You Take It, Talk About It." The campaign has utilized a consensus report, electronic media messages, print media messages, and direct-to-consumer brochures to reach health professional and consumer target audiences nationwide.

During 1988, 450 television stations, including CBS-TV, ran the television PSA. The program "20/20" broadcast a segment on prescription medicines on October 28, 1988; it mentioned NCPIE and listed the five questions. One thousand radio stations received both taped and script copies of the radio PSA, and Mutual Broadcasting System aired it. Print ads have appeared in *JAMA, New England Journal of Medicine, Medical Economics, American*

Pharmacy, NARD Journal, Pharmacy West, AMA News, Juvenile Diabetes, Newsweek, People Magazine, and *U.S. News and World Report.*

IV. Work Site Initiative

To expand the distribution of the Get the Answers campaign, the Exxon Foundation awarded NCPIE a grant to conduct the Get the Answers Work Site Initiative. This initiative is designed to encourage corporations to distribute Get the Answers materials to their employees, retirees, and customers. This Work Site Initiative includes a packet of information with items such as a sample newsletter or magazine article, sample letter to employees, and poster art to assist companies in implementing this campaign.

NCPIE distributed the Get The Answers work site kits to organizations such as Washington Business Group on Health, Business Roundtable, Business Coalitions Clearinghouse, and U.S. Chamber of Commerce. As a result, articles on the Get the Answers campaign appeared in such publications as *Executive Reports* that is sent to senior management of all the health insurance companies; the Metropolitan Life Insurance Company's newsletter, *Health Action;* and *Alumni News* magazine (circulation of over 65,000).

Also, the Prudential Insurance Company reproduced and distributed NCPIE patient education materials, including the medical data wallet card, to its active and retired employees. In addition, an issue of *AOMA Reports* (American Occupational Medical Association) contained an article with information on ordering the cards.

In 1989 NCPIE plans to seek additional funds to implement this campaign nationally. It is revising the campaign kit to include updated resource listings and a print advertisement. NCPIE plans to market the campaign to Fortune 500 companies, the insurance industry, managed health care facilities, business and in-flight magazines, etc.

V. Urging Health Professionals To Provide Information

Concurrent with the activities aimed at patients, FDA and many other organizations are conducting a major campaign to encourage health professionals to provide information to their patients. Urging consumers to "get the answers" and health professionals to "give the answers" is vital to bridge the communications gap -- to get both sides to talk to each other.

The NCPIE Give the Answers campaign asks health professionals to take the initiative in giving patients the information they need to use prescription drugs safely and effectively. The initial thrust of this campaign was the distribution of a source book for the professional that provided descriptions, illustrations, and ordering information for a selected set of prescription drug leaflets, booklets, and books appropriate for patient counseling. These source books were distributed to physicians at an American College of Cardiology meeting and to pharmacists at the annual meeting of the American Pharmaceutical Association.

FDA supported the Give the Answers campaign by developing a health professional exhibit program to reach practicing health professionals. The program has been displayed at a number of national health conferences and has been well received by the attendees. FDA also conducted a number of patient education programs with health professional organizations.

The Give the Answers campaign was also designed to involve nurses. NCPIE has produced a TV PSA encouraging consumers to ask their nurses for information about prescription drugs. The American Nurses Association, the National League for Nursing, the Nurses Association of the American College of Obstetricians and Gynecologists, and the Oncology Nursing Society actively promoted the PSA in their communities. In addition, many professional nursing journals promoted the availability of the NCPIE booklet entitled *A Sourcebook for Nurses: Counseling Patients About their Medicines*.

In 1986 the Give the Answers print advertisement was featured prominently in the May 1986 *Medical Times* special issue on patient education. Also, Winthrop Breon Laboratories (Sterling Drug) distributed 39,000 Talk About Prescriptions posters to physicians and hospital pharmacists through its detail sales force. The *FDA Drug Bulletin* alerted physicians to Talk About Prescriptions Month and the possibility that their patients might ask questions regarding their medicines.

In 1986 the American Pharmaceutical Association and the Pharmaceutical Manufacturers Association (PMA) launched a major patient compliance campaign with the theme "Your Health Is In Your Hands." The campaign, aimed at the one-third of the population that improperly takes medicines, includes TV and radio PSAs, a film, posters, fliers, and print ads to health professionals and focuses on how and when to take drugs.

In addition to FDA and NCPIE efforts, many health professional and private sector groups have developed and are continuing to promote specific drug information systems to help health professionals provide prescription drug information to their patients. For example:

The United States Pharmacopeia (USP) produces a comprehensive source of information on drugs in the form of United States Pharmacopeia Dispensing Information (USP DI) and drug specific patient information sheets.

The American Medical Association (AMA) utilizes the USP data base for its Patient Medication Instruction (PMI) leaflet program. Eighty-two different leaflets are currently available.

The American Academy of Family Physicians released an updated version of its DUET (Drug Use Education Tips) program in 1988. Based on USP DI (Advice for the Patient), the new DUET contains abstractions for 315 of the monographs included in USP DI. The format of each drug entry has been changed to include selected commonly-used brand names.

The National Association of Retail Druggists utilizes the USP data base for its Patient Information Leaflets Program -- 48 leaflets covering approximately 200 generic entities are currently available.

The American Dental Association is promoting a series of information leaflets for drugs used in dentistry.

Medical Strategies, Inc., in cooperation with USP, is promoting a Pharmacy Information Center, which will allow customers in a pharmacy, hospital, clinic, or group practice setting to receive, via a video terminal set up in a kiosk, information about the drugs that are being prescribed for them.

The American Society of Hospital Pharmacists published the 1988 edition of *American Hospital Formulary Service Drug Information* (*AHFS Drug Information*), a drug-information reference containing approximately 100 comprehensive, up-to-date monographs with information on tens of thousands of products (virtually every single-drug entity available in the United States).

VI. Monitoring Patient Education Activities

FDA and others are continuing to evaluate the effectiveness of patient education programs and are monitoring the attitudes and behavior of consumers and health professionals about patient information. In this regard, FDA has conducted surveys on consumers' attitudes and experiences, and NCPIE and the Pharmaceutical Manufacturers Association have produced directories of drug information programs and resources. Details of the activities follow.

In 1985 FDA conducted a survey of consumers' attitudes and experiences regarding prescription drug information. This survey was a follow-up to a 1982 survey on the same topic and contained an in-depth section on what encourages or discourages questions from consumers to their health professionals.

In 1986 FDA completed a segmentational analysis of data from this 1985 survey. Four types of respondents were identified, based on their methods of obtaining information about their medications.

More than 34 percent were classified as "uninformed"; they were unlikely to receive written information about their medications from their doctor or their pharmacist and appeared unmotivated to seek information from any source. Other groups received counseling from their physicians and pharmacists or used sources such as reference books, magazines, and friends for drug information. It is the "uninformed" group that the study's authors saw as most in need of motivational messages to learn more about prescription drugs. "These individuals may not recognize the problems that may occur if drugs are used improperly, nor may they perceive the need for their own vigilance and concern when taking medica- tion."

The survey results suggest that the Get the Answers consumer education campaign and the Give the Answers professional education campaign are accurately based on strongly-held and documented consumer perceptions. As a result, the campaigns have focused on using appropriate techniques and mechanisms to improve the flow of information between patient and health professional, and urging health professionals to use written information to reinforce medication counseling.

In 1985 NCPIE released a *Directory of Prescription Drug Information and Education Programs and Resources*. This directory, done with the assistance and cooperation of FDA, is intended to assist organizations and health professionals in the development of new prescription drug information and education programs/materials appropriate to their settings and audiences. It lists 184 programs being conducted by a wide range of organizations such as the Arthritis Foundation, American Association of Retired Persons, National Cancer Institute, various pharmaceutical companies, drug chains, and pharmacy schools. The directory is currently under revision and an updated version is scheduled to be completed in 1989.

The PMA has developed a directory entitled *Sources* that is designed to inform consumers about health information materials available from member companies. Nearly 400 different sources are listed in this indexed catalogue that covers a broad range of topics including preventive health, understanding disease processes, and specific information about pharmaceutical products. The directory allows consumers to order patient education materials from PMA member companies.

The March 20-23, 1988, Surgeon General's Workshop on Health Promotion and Aging recommended that the health care community increase its efforts to inform and educate older Americans about prescription drugs. The medical working group recommendations include: expanding the role of pharmacists as partners with physicians; educating patients to maintain their own drug profiles; training families, community members, and others who care for older people in their homes; adding instruction in counseling older people to all professional curricula; and providing third-party reimbursement for medication counseling.

A 1988 study led by Dr. Suzanne Thompson, a psychologist at Pomona College in California, found that by preparing three questions to ask before entering the doctor's office, patients can improve the chances that they will feel satisfied with the visit. These findings were supported by a 1988 study by Dr. Herman Feiffel, a psychologist at a Veterans Administration clinic in Los Angeles. Dr. Feiffel found that patients who confronted medical problems fared better than those who tended to avoid facing the problems or who passively accepted them.

FDA continues to be encouraged by the number and quality of patient education activities undertaken by the various sectors. FDA will continue to provide resources and leadership to foster the patient education initiative.

X-RAY INITIATIVES

Since 1980 FDA has also promoted improved communications between patients and practitioners regarding the x rays being prescribed for them. FDA pursued this goal by initiating the public education campaign, "X rays: Get the Picture on Protection." The campaign is designed to assist patients in taking a more active role in their health care involving medical x rays. The patient is encouraged to ask the physician or dentist why an x ray is needed and whether a gonad shield can be used, inform the doctor of the possibility of pregnancy, keep a record of x rays taken, and share this information with the health professional. A key part of this campaign is a wallet card that helps patients keep track of their x rays and provides a convenient record for sharing with their healthcare providers.

In 1987 FDA initiated an education program for both physicians and women patients, instructing them on how to select good mammography facilities. The program recommended selecting facilities that employ x-ray technologists and radiologists specially trained in mammography; using "dedicated" mammography equipment; and assuring that x-ray equipment is inspected and calibrated annually.

Two consumer articles were widely circulated. The first, "Why Women Don't Get Mammograms (And Why They Should)," was published in the May 1987 *FDA Consumer*. The second article, "Important Information About Mammography Screening for Breast Cancer," was disseminated to 120 editors of national women's magazines and through the North American Precis Syndicate to 1,000 daily and 2,800 weekly suburban newspapers. An exhibit entitled "Improving Image Quality and Reducing Radiation Exposure in Mammography" was developed for health practitioners and displayed at national and state medical meetings.

In 1988 FDA sent a Dear Consumer letter on the importance of mammography to more than 7,000 consumers interested in women's health issues, including individuals, hospitals, women's health centers, state and local health departments, health professionals, and the media.

In July 1988 a five-part series on mammography was sent via satellite to 650 TV stations throughout the United States.

MEDICAL DEVICES INITIATIVES

In addition to the prescription drug education and x-ray initiatives, FDA has been involved in numerous medical device patient education activities over the past several years. Some of these initiatives were developed in response to a need demonstrated by consumer inquiries to FDA's field and headquarters offices. Others were initiated because of recent developments in medical devices, problems with particular devices, and/or new recommended technologies designed to minimize health risks and improve health care. These medical device patient education initiatives have included programs on women's health care devices, intrauterine contraceptive devices, tampons and toxic shock syndrome, and hearing aids.

FDA has implemented an education program on Women's Health Care Devices to provide consumers with specific information on the proper use, benefits, and risks associated with these products. The program emphasizes the importance of consulting with physicians about health problems or concerns and discussing the use of any medical devices women may be using or considering. It also encourages consumers to request patient information materials from their health care providers. Topics covered in the women's health care device program include: menstrual products, birth control devices, diagnostic/monitoring devices, breast reconstruction/augmentation, facial reconstruction, and epilation devices.

In 1982 FDA implemented a nationwide educational program on tampons and Toxic Shock Syndrome. In 1985 the Agency developed a poster-format learning unit (endorsed by the American Association for the Advancement of Health Education and the American Academy of Family Physicians) to reach adolescent females. FDA and the American College of Obstetricians and Gynecologists distributed the poster to secondary schools, young women's organizations, health professionals, and health administrators/educators.

In 1986 FDA developed consumer education materials on home-use diagnostic devices. A February 1986 FDA Consumer article, "Do-It-Yourself Medical Testing," stressed the need for patients to maintain communication with their health care providers when selecting and using diagnostic testing devices. FDA distributed information concerning home-use diagnostic devices to health writers/editors of popular newspapers and magazines and requested that they use these materials in developing articles. This information also stressed the need for patients to maintain communication with their health care providers.

In 1987 FDA implemented a nationwide secondary school education program on the ill effects of exposure to ultraviolet radiation via indoor tanning devices. Although often promoted as "risk free," tanning devices that emit primarily ultraviolet-A (UV-A) radiation pose many of the same health risks that ultraviolet-B (UV-B) tanning devices and suntanning present. These risks include cataracts in eyes not protected with properly fitted UV-absorbing goggles, photosensitive reactions resulting in severe skin burns, premature aging of the skin, and the suppression of certain immune system responses. Studies conducted by FDA in 1986 demonstrated the carcinogenic potential of U-VA tanning devices.

To counter the public's misconception that these devices are "safer than the sun," FDA developed a consumer education program which includes a poster learning unit for secondary schools entitled "The Darker Side of Indoor Tanning." In May 1987 the poster was mailed to 46,000 school nurses and health teachers in every U.S. high school. In July 1988 the poster and a companion brochure were mailed to all U.S. college health educators and health administrators. A slide show for use by FDA Consumer Affairs Officers and other FDA staff was produced in August 1988 to complement the indoor tanning program. In September 1988 FDA broadcast a video news release to TV stations across the country to warn about the hazards of indoor tanning.

Also in 1988, two additional professional associations endorsed the poster learning unit segment of the program. Endorsers now include the American Academy of Dermatology, the American Cancer Society, the American Society of Plastic and Reconstructive Surgeons, the American Academy of Family Physicians, the American Academy of Ophthalmology, and the Health Physics Society.

In March 1986 the Senate Special Committee on Aging held hearings on concerns about the safety and efficacy of dialysis treatments using new and reused dialysis devices. Following the hearings, a task force was established to develop an implementation plan based on the recommendations and concerns expressed at the congressional hearings. The task force determined there was a need for the public to be better informed about the potential benefits and risks of the reuse of hemodialysis equipment so that patients could make more informed decisions about their health care.

In order to better access the information needs of patients with regard to reuse of hemodialysis equipment, in March 1988 the Center for Devices and Radiological Health conducted a nationwide telephone survey of hemodialysis patients. The survey was meant to measure patients' knowledge and perception with regard to hemodialysis reuse based on information they had already received on the subject. There were 480 patients who completed interviews: 271 said they were on "reuse," 170 said they were on "single use," and 39 said they did not know which they were on.

Although most of the patients surveyed said they were comfortable with what they knew about their treatment and had a good understanding of the information received, most could not identify the benefits or risks of reuse. Those who requested additional information said they wanted it to address reuse in general, how the equipment works, dialysis research and development, new drugs, and financial aid.

Based on these findings and the fact that most patients indicated they depend on their physicians and other health care providers for information, the Center concluded its role should be to foster the development of patient information by these providers. The Center plans to publish a report on the survey in a dialysis journal and/or in one of its own publications in early 1989.

During 1987 and 1988, FDA produced a variety of messages for the public about the risks of improperly using homemade saline, including two Talk Papers, Drug and Device Bulletin articles, a newspaper article distributed by the North American Precis Syndicate, an *FDA Consumer* update, and articles in the trade and ophthalmic professional press. These activities followed a study completed by the Centers for Disease Control in July 1987 which demonstrated an association between homemade saline and a rare but serious eye infection, *Acanthamoeba Keratitis*.

On January 24, 1989, FDA issued a safety alert to 50,000 practicing ophthalmologists, optometrists, and opticians in the United States to share with patients who may use homemade saline solutions for soft contact lenses. Homemade saline is made from salt tablets and distilled water and may become contaminated with harmful microorganisms that can cause serious and painful eye infections if improperly used. In some severe cases this has lead to blindness. The alert included a patient information sheet which describes the proper use of homemade saline and cautions against improper uses.

In addition, on February 15, 1989, FDA broadcast a satellite video news release and issued a press release about homemade saline. The Agency also published an *FDA Drug Bulletin* (February issue) and an *FDA Consumer* update and sent copies of the alert letter to editors of pharmacy and health newsletters.

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For further information on patient education activities you may contact one or more of the following offices:

General information on present and future prescription drug patient education activities:
Kenneth T. Durham, Deputy Associate Commissioner for Consumer Affairs, HFE-2
FDA, Office of Consumer Affairs
(301) 443-5006

Activities involving health professional associations:
Robert V. Veiga, M.D., Director, Medicine Staff
FDA, Office of Health Affairs, HFY-40
(301) 443-5470

Medical devices and x-ray patient education activities:
Diana R. Woods, Director, Division of Consumer Affairs
Office of Training and Assistance, HFZ-210
FDA, Center for Devices and Radiological Health
(301) 443-5190

Patient education research:
Louis A. Morris, Ph.D., Acting Director, Division of Drug Advertising and Labeling, HFD-246
FDA, Center for Drug Evaluation and Research
(301) 443-5373

Resource and referral center on patient information and source of patient education materials:
Fran Rowland, Technical Information Assistant
Division of Drug Advertising and Labeling, HFD-246
FDA, Center for Drug Evaluation and Research
(301) 443-5373

Patient education activities being held in local areas:
FDA Consumer Affairs Officers
Look in the telephone directory under "U.S. Government, Health and Human Services Department, Food and Drug Administration." If it does not appear, contact:

Claudette T. Guilford, Director
Consumer Affairs and Information Staff
FDA, Office of Regional Operations
5600 Fishers Lane, HFC-110, Rockville, MD 20857
(301) 443-4166

NCPIE activities:
Robert Bachman, Executive Director
National Council on Patient Information and Education
666 Eleventh Street, NW, Suite 810
Washington, DC 20001
(202) 347-6711

1987

Prescription Drug, Medical Device, and X Ray Patient Education Activities

Status Report - December 1987

OVERVIEW

To assure that prescription drugs and medical devices are used properly, FDA coordinates the development and implementation of major patient education initiatives in the public and private sectors. Since the early 1980s FDA has placed emphasis on patient education programs for prescription drugs and x rays. Activities were also conducted with women's health care devices and hearing aids. These initiatives have been concentrated in three main areas: urging patients to request information; encouraging health professionals to provide information; and monitoring patient education activities.

The prescription drug initiatives began in 1982 with the formation of the National Council on Patient Information and Education (NCPIE). The results of an FDA survey, completed that year, indicated that most patients were not given sufficient information when they received a prescription.

In 1983 FDA and NCPIE launched the "Get the Answers" campaign urging patients to ask their health professionals questions about their prescriptions. The "Get the Answers" message was widely disseminated to consumers and health professional organizations through news releases, advice columns, and multiplier groups. FDA also worked with the Social Security Administration to disseminate the "Get the Answers" message to 36 million social security recipients. In 1983 several private sector organizations (the American Medical Association, the U.S. Pharmacopeia, and the American Association of Retired Persons) developed patient drug leaflet systems for health professionals to use with their patients.

In 1984 FDA conducted a successful "Ask the Doctor about Prescription Drugs" Day in cooperation with the American Academy of Family Physicians and "Call for Action." FDA received the National Association of Consumer Agency Administrators' 1985 "Best Program Award" for this initiative which was conducted in cities across the country. Also in 1984, NCPIE and FDA launched a "Give the Answers" campaign to encourage health professionals to utilize the drug information systems that were available.

In 1985 FDA and other organizations targeted prescription drug patient education efforts to two major groups: the elderly, who take more drugs per capita than do younger individuals in proportion to their representation in the population; and Hispanics, who are often unreached by English language campaigns. Also, NCPIE launched the "Work Site Initiative" which is designed to encourage corporations to disseminate the "Get the Answers" campaign materials to their employees and customers.

In 1986 FDA participated in the first national "Talk About Prescriptions" Month sponsored by NCPIE. The second annual "Talk About Prescriptions" Month campaign was conducted during October 1987. Also during 1987 there was increased participation by business, health organizations, and state and local governments in patient education activities.

In 1987 NCPIE announced a public education campaign to improve communications between health professionals and the elderly. The campaign consists of a 30-second TV PSA, a 30-second radio PSA, a color brochure, and print ads for consumer and professional publications.

The Agency is also continuing its nationwide diagnostic x ray public information campaign which began in 1980. The goal of the campaign is to stimulate consumers to take an active role in their health care to assure that they receive the maximum benefit with the minimum risk of diagnostic x rays. Over the years FDA has initiated campaigns in the areas of scoliosis, mammography, intrauterine contraceptive devices, toxic shock syndrome, home-use diagnostic devices, and indoor tanning devices.

Virtually all FDA offices and staffs have conducted activities in support of FDA's and NCPIE's patient education initiative. A list of contact people appears at the end of the status report.

PRESCRIPTION DRUG INITIATIVES

I. Urging Patients to Request Information

The "Get the Answers" campaign is the primary education program urging patients to ask their health professionals questions about their prescription drugs. FDA, NCPIE, and various other organizations initiated this public communications effort in July 1983. The major component of the campaign is a medical data wallet card that lists the five questions patients should ask when they get a prescription. These questions are:

1. What is the name of the drug and what is it supposed to do?
2. How and when do I take it -- and for how long?
3. What foods, drinks, other medicines, or activities should I avoid while taking this drug?
4. Are there any side effects, and what do I do if they occur?
5. Is there any written information available about the drug?

FDA, NCPIE, and many other organizations helped disseminate the "Get the Answers" message to millions of consumers. For example, FDA worked with the Social Security Administration, the Veterans Administration, and the Consumer Information Center to offer FDA materials on the proper use of medication to over 40 million consumers whom these organizations contact each year.

FDA also has targeted the "Get the Answers" message to specific populations, such as Hispanics and the elderly. There are over 15 million Hispanic consumers in the continental United States. Due to language and cultural differences, a large portion of this population may not be reached by traditional patient education messages.

In order to reach Hispanics FDA has conducted the following initiatives: worked with the National Coalition of Hispanic Health and Human Services Organizations (COSSMHO) to translate the medical data wallet card into Spanish; joined with groups such as the National Hispanic Council on Aging to distribute these cards to Spanish-speaking consumers; presented three conferences to promote interest and support for incorporating patient education into Puerto Rico's public and private school curricula; and worked with groups such as the Latin Chamber of Commerce to develop and coordinate a Hispanic patient education program in Florida.

In addition to continuation of the "Get the Answers" campaign, several new initiatives were conducted to encourage patients to request information about their prescriptions. These initiatives are described below.

II. "Talk About Prescriptions" Month

In 1986 NCPIE and FDA initiated the first national "Talk About Prescriptions" Month. The purpose of the month was to stimulate activity to motivate health professionals to give, and consumers to seek, the information needed for safe and effective medication use. DHHS Assistant Secretary for Health Robert Windom and FDA Commissioner Frank Young joined NCPIE Chairman Paul Rogers at the NCPIE press conference on October 2, 1986 to announce the campaign. NCPIE developed and distributed a campaign newspaper ("Talk About Prescriptions") that was designed as a do-it-yourself kit containing available materials/resources to support activities planned during October.

Based on the success of the first "Talk About Prescriptions" Month, NCPIE decided to make it an annual event. During October 1987 the second "Talk About Prescriptious" Month emphasized the problem of improper medication use among the elderly. Once again FDA and NCPIE held a press conference to:

1. Kick off "Talk About Prescriptions" Month,
2. Officially release the NCPIE report on improper medication use among older people, and
3. Announce the new public education campaign on improving communications between health professionals and the elderly.

The public education campaign consists of: a 30-second TV public service announcement, a 30-second radio public service announcement, a four color brochure, and print ads for consumer and professional publications. The campaign focuses on effective communication between the older patient and the health care professional as the way to reduce medication misuse. Media materials -- using the slogan "Before You Take It, Talk About It" -- urge older consumers to talk with doctors, pharmacists, and nurses about the medicines prescribed for them. Four hundred fifty TV stations ordered the 1987 elderly PSA. The CBS network utilized the ad extensively during October, November, and December.

FDA distributed the "Talk About Prescriptions" Month campaign newspaper to newsletter editors, health professional organizations, and several thousand consumers and multiplier organizations. FDA urged these groups to sponsor activities in support of the month; many indicated that they would. National groups, such as National Geriatrics Society and local organizations, such as the District of Columbia Department of Consumer and Regulatory Affairs, conducted special programs and classes, gave speeches, prepared press releases, public service announcements or telephone tapes, or distributed posters and brochures. In addition, the governors from several states signed proclamations to honor national "Talk About Prescriptions" Month. The Administration on Aging also distributed 60,000 copies of the 1987 NCPIE "Talk About Prescriptions" campaign newspaper nationwide to organizations which work with the elderly.

Articles promoting the month were included in the October 1987 FDA Consumer, Pharmacy Times, FDA Drug Bulletin and numerous other publications.

NCPIE placed emphasis on the elderly because the elderly use more prescription drugs per capita than the rest of the population. While those 65 and over constitute about 11 percent of the total population, they take about 25 percent of all drugs dispensed in the United States, both prescription and over the counter. The fact that the elderly must take so many medications increases their chances of experiencing adverse reactions.

III. "Work Site Initiative"

To expand the distribution of the "Get the Answers" campaign, NCPIE was awarded a grant from the Exxon Foundation to conduct the "Get the Answers Work Site Initiative." This initiative is designed to encourage corporations to distribute "Get the Answers" materials to their employees, retirees, and customers. This "Work Site Initiative" includes a packet of information with items such as a sample newsletter or magazine article, sample letter to employees, and poster art that have been developed to assist companies in implementing this campaign.

NCPIE distributed the "Get the Answers" worksite kits to such organizations as Washington Business Group on Health, Business Roundtable, Business Coalitions Clearinghouse, and U.S. Chamber of Commerce. As a result, articles on the "Get the Answers" campaign appeared in publications such as Executive Reports that goes to senior management of all the health insurance companies, the Metropolitan Life Insurance Company's newsletter, Health Action, and Alumni News magazine, with a circulation of over 65,000.

Also, the Prudential Insurance Company reproduced and distributed NCPIE patient education materials, including the medical data wallet card, to their active and retired employees. In addition, an issue of AOMA Reports (American Occupational Medical Association) contained an article with ordering information.

IV. Urging Health Professionals To Provide Information

Concurrent with the activities aimed at patients, FDA and many other organizations are conducting a major campaign to encourage health professionals to provide information to their patients. Urging consumers to "Get the Answers" and health professionals to "Give the Answers" is vital to bridge the communications gap -- to get both sides to talk to each other.

The NCPIE "Give the Answers" campaign is asking health professionals to take the initiative in giving patients the information they need to use prescription drugs safely and effectively. The initial thrust of this campaign was the distribution of a source book for the professional that provided descriptions, illustrations, and ordering information for a selected set of prescription drug leaflets, booklets, and books appropriate for patient counseling. These source books were distributed to physicians at an American College of Cardiology meeting and to pharmacists at the annual meeting of the American Pharmaceutical Association.

FDA supported the "Give the Answers" campaign by developing a health professional exhibit program to reach the practicing health professional. The program has been displayed at a number of national health conferences and has been well received by the attendees. FDA also conducted a number of patient education programs with health professionals such as a special conference at Howard University and a presentation for the Area Health Education Centers.

The "Give the Answers" campaign was also designed to involve nurses. NCPIE has produced a TV public service announcement encouraging consumers to ask their nurses for information about prescription drugs. The American Nurses' Association, the National League for Nursing, the Nurses' Association of the American College of Obstetricians and Gynecologists, and the Oncology Nursing Society actively promoted the public service announcement in their communities. In addition, many professional nursing journals promoted the availability of the NCPIE booklet entitled, "A Sourcebook for Nurses: Counseling Patients About Their Medicines."

In 1986 the "Give the Answers" print advertisement was featured prominently in the May 1986 Medical Times special issue on patient education. Also Winthrop Breon Laboratories (Sterling Drug) distributed 39,000 "Talk About Prescriptions" posters to physicians and hospital pharmacists through its detail sales force. The FDA Drug Bulletin alerted physicians to "Talk About Prescriptions" Month and the possibility that their patients might ask questions regarding their medicines.

In 1986 the American Pharmaceutical Association and the Pharmaceutical Manufacturers Association launched a major patient compliance campaign. The campaign, aimed at the one third of the population that improperly takes medicines, includes TV and radio PSAs, a film, posters, fliers, and print ads to health professionals. The theme is "Your Health Is In Your Hands." This campaign is considered to be ancillary to NCPIE, focusing primarily on how and when to take drugs.

In addition to FDA and NCPIE efforts, many health professional and private sector groups have developed and are continuing to promote specific drug information systems to help health professionals provide prescription drug information to their patients. For example:

The United States Pharmacopeia (USP) produces a comprehensive source of information on drugs in the form of United States Pharmacopeia Dispensing Information and drug specific patient information sheets.

The American Medical Association utilizes the USP data base for its Patient Medication Instruction (PMI) leaflet program. Eighty-two different leaflets are currently available. In 1987 AMA became a NCPIE member (previously a liaison member).

The American Academy of Family Physicians is promoting an improved version of its Drug Use Education Tips (DUET) program. The program consists of sets of 300 monograph abstractions printed in loose leaf form so that physicians can photocopy appropriate pages for their patients.

The National Association of Retail Druggists utilizes the USP data base for its Patient Information Leaflets Program -- 48 leaflets covering approximately 200 generic entities are currently available.

The American Dental Association is promoting a series of drug leaflets for those drugs used in dentistry.

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V. Monitoring Patient Education Activities

FDA and others are continuing to evaluate the effectiveness of patient education programs and are monitoring the attitudes and behavior of consumers and health professionals about patient information. In this regard, FDA has conducted surveys on consumers' attitudes and experiences, and NCPIE and the Pharmaceutical Manufacturers Association have produced directories of drug information programs and resources. Details of the activities follow.

In 1985 FDA conducted a survey of consumers' attitudes and experiences regarding prescription drug information. This survey was a follow-up to a 1982 survey on the same topic and contained an in-depth section on what encourages or discourages questions from consumers to their health professionals.

In 1986 FDA completed a segmentational analysis of data from this 1985 survey. Four types of respondents were identified, based on their methods of obtaining information about their medications.

More than one out of three respondents (34 percent) were classified as "uninformed"; they were unlikely to receive written information about their medications from their doctor or their pharmacist, and appeared unmotivated to seek information from any source. Other groups received counseling from their physicians and pharmacists, or used sources such as reference books, magazines, and friends for drug information. It is the "uninformed" group that the study's authors saw as most in need of motivational messages to learn more about their prescription drugs. "These individuals may not recognize the problems that may occur if drugs are used improperly, nor may they perceive the need for their own vigilance and concern when taking medication."

The survey results suggest that the "Get the Answers" consumer education campaign and the "Give the Answers" professional education campaign are accurately based on some strongly held and documented consumer perceptions. As a result, the campaigns have focused on using appropriate techniques and mechanisms to improve the flow of information between patient and health professional, and urging health professionals to use written information to reinforce medication counseling.

In 1985 NCPIE released a Directory of Prescription Drug Information and Education Programs and Resources. This directory, done with the assistance and cooperation of the FDA, is intended to assist organizations and health professionals in the development of new prescription drug information and education programs/ materials appropriate to their settings and audiences. It lists 184 programs being conducted by a wide range of organizations such as the Arthritis Foundation, American Association of Retired Persons, National Cancer Institute, various pharmaceutical companies, drug chains, and pharmacy schools. The directory is currently under revision and an updated version is scheduled to be completed in 1988.

The Pharmaceutical Manufacturers Association has developed a directory entitled Sources that is designed to inform consumers about health information materials available from member companies. Nearly 400 different sources are listed in this indexed catalogue that covers a broad range of topics including preventive health, understanding disease processes, and specific information about pharmaceutical products. The directory allows consumers to order patient education materials from PMA member companies. FDA continues to be encouraged by the number and quality of patient education activities undertaken by the various sectors. FDA will continue to provide resources and leadership to foster the patient education initiative.

X-RAY INITIATIVES

Since 1980 FDA has also promoted improved communications between patients and practitioners regarding the x rays being prescribed for them. FDA pursued this goal by initiating the public education campaign, "X rays: Get the Picture on Protection." The campaign is designed to assist patients in taking a more active role in their healthcare involving medical x rays. The patient is encouraged to ask the physician or dentist why an x ray is needed, ask whether a gonad shield can be used, inform the doctor of the possibility of pregnancy, keep a record of x rays taken, and share this information with the health professional. A key part of this campaign is a wallet card that helps patients keep track of their x rays and provides a convenient record for sharing with their healthcare providers.

Another x-ray campaign initiated during 1985 concerned reducing radiation exposure during scoliosis radiography. The objectives of this program are to make parents and health professionals aware of the:

- potential health risks (especially to adolescent females) associated with repeated radiation exposure to developing breast tissue;
- recommended methods available to significantly reduce radiation exposure without compromising the quality of the x-ray image; and
- importance of speaking to their doctors about what radiation reduction methods will be used to minimize health risks from excessive exposure when their children are x rayed.

FDA published detailed information on scoliosis radiography for both health professionals and consumers. Available for health professionals are: a report, "Patient Exposure Reduction During Scoliosis Radiography;" a pamphlet, "Reducing Patient Exposure During Scoliosis Radiography;" a videotape, slides/script, and a nomadic exhibit; and for consumers: an FDA Consumer reprint, "When the Spine Curves," and a tabletop exhibit.

In 1987 several stimuli were responsible for raising public awareness about the benefits of early detection of breast cancer through the use of mammography. In large part, this was due to media coverage of prominent women treated for breast cancer, commercials and PSAs encouraging women 35 and older to seek mammography for early breast cancer detection, and the American Cancer Society's emphasis on low cost mammography through its 1987 national cancer screening program. In addition to working with the radiological community and the industry to improve the quality of mammography, FDA initiated an education program for both physicians and women patients, instructing them on how to select good mammography facilities. The program recommends selecting facilities that employ x-ray technologists and radiologists specially trained in mammography; using "dedicated" mammography equipment; and assuring that x-ray equipment is inspected and calibrated annually.

Two consumer articles were widely circulated. The first, "Why Women Don't Get Mammograms (And Why They Should)," was published in the May 1987 FDA Consumer. The second article, "Important Information About Mammography Screening for Breast Cancer," was disseminated to 120 editors of national women's magazines and through the North American Precis Syndicate to 1,000 daily and 2,800 weekly suburban newspapers. An exhibit entitled "Improving Image Quality and Reducing Radiation Exposure in Mammography" was developed for health practitioners and displayed at several national and state medical meetings during 1987. An article was written to help physicians refer their patients to adequate mammography facilities, and will be submitted to a major medical journal.

MEDICAL DEVICES INITIATIVES

In addition to the prescription drug education and x-ray initiatives, FDA has been involved in numerous medical device patient education activities over the past several years. Some of these initiatives were developed in response to a need demonstrated by consumer inquiries to FDA's field and headquarters offices. Others were initiated because of recent developments in medical devices, problems with particular devices, and/or new recommended technologies designed to minimize health risks and improve health care.

These medical device patient education programs have included: an education program to provide consumers with specific information on the proper use, benefits, and risks associated with women's health care devices; programs to inform consumers about intrauterine contraceptive devices (IUDs); a program about tampons and toxic shock syndrome (TSS); a program to inform health professionals and the general public about the safe and effective use of hearing aids; and an ongoing program on what constitutes good mammography.

Over the past several years, FDA implemented a consumer education program on Women's Health Care Devices. The objective of the program was to provide consumers with specific information on the proper use, benefits, and risks associated with women's health care devices to better enable them to assume an active role in their own health care. The program emphasizes the importance of consulting with physicians about health problems or concerns and discussing the use of any medical device women may be using or considering. It also encourages consumers to request patient information materials from their health care providers. Topics covered in the women's health care device program include: menstrual products, birth control devices, diagnostic/monitoring devices, breast reconstruction/ augmentation, facial reconstruction, and epilation devices.

Specific consumer education programs containing information on the IUD were implemented. These programs encouraged women to discuss with their physicians the risks and benefits associated with IUD use.

To keep women and physicians apprised of new evidence and scientific findings associated with IUD use, e.g., the high incidence of pelvic inflammatory disease in IUD wearers, FDA has issued many messages to the public and to the health care community by way of Drug Bulletin articles, press releases, talk papers, and FDA Consumer articles.

In 1982 FDA implemented a nationwide educational program on tampons and Toxic Shock Syndrome (TSS). In 1985 the Agency developed a poster-format learning unit (endorsed by the American Association for the Advancement of Health Education and the American Academy of Family Physicians) to reach adolescent females. The poster was distributed by FDA and the American College of Obstetricians and Gynecologists to secondary schools, young women's organizations, health professionals, and health administrators/educators. The program focused on the symptoms of TSS, what to do if symptoms occur, and the need to discuss symptoms and the proper use of tampons with physicians.

FDA was successful in getting the Centers for Disease Control to include TSS information in their "Teenage Health Teaching Modules" developed for secondary school health curricula.

In 1986 FDA also initiated consumer education materials on home-use diagnostic devices. A February 1986 FDA Consumer article, "Do-It-Yourself Medical Testing," stressed the need for patients to maintain communication with their health care providers when selecting and using diagnostic testing devices. FDA distributed information concerning home-use diagnostic devices to health writers/editors of popular newspapers and magazines and requested that they use these materials in developing articles. This information also stressed the need for patients to maintain communication with their health care providers.

In 1987, FDA implemented a nationwide secondary school education program on the ill effects of exposure to UV radiation via indoor tanning devices. Although often promoted as "risk free," tanning devices that emit primarily ultraviolet-A (UVA) radiation pose many of the same health risks that ultraviolet-B tanning devices and suntanning present. These risks include cataracts in eyes not protected with properly fitted UV-absorbing goggles, photosensitive reactions resulting in severe skin burns, premature aging of the skin, and the suppression of certain immune system responses. Studies conducted by FDA in 1986 demonstrated the carcinogenic potential of UVA tanning devices. To counter the public's misconception that these devices are "safer than the sun," FDA developed a consumer education program which includes a poster learning unit for secondary schools entitled "The Darker Side of Indoor Tanning." In May 1987 the poster was mailed to 46,000 school nurses and health teachers, covering every U.S. high school, and approximately 42,000 copies of a companion brochure were distributed to consumers during 1987. The American College of Dermatology reprinted the poster at their expense, distributed it to their 8,000 members, and encouraged them to offer their services to local schools as guest speakers in support of the program. FDA also developed four nomadic exhibits for headquarters and field use in promoting the program.

For further information on patient education activities you may contact one or more of the following offices:

General information on present and future prescription drug patient education activities:
Kenneth Durham, Deputy Associate Commissioner for Consumer Affairs, HFE-2
FDA, Office of Consumer Affairs
(301) 443-5006

Activities involving health professional associations:
Robert V. Veiga, M.D., Director, Medicine Staff
FDA, Office of Health Affairs, HFY-40
(301) 443-5470

Medical devices and x-ray patient education activities:
Diana R. Woods, Director, Division of Consumer Affairs
Office of Training and Assistance, HFZ-210
FDA, Center for Devices and Radiological Health
(301) 443-4190

Patient education research:
Louis A. Morris, Ph.D., Acting Director, Division of Drug Advertising and Labeling, HFN-246
FDA, Center for Drugs and Biologics
(301) 443-5373

Resource and referral center on patient information and source of patient education materials:
Fran Rowland, Technical Information Assistant
Patient Education Resource Center, Division of Drug Advertising and Labeling, HFN-246
FDA, Center for Drugs and Biologics
(301) 443-5373

Patient education activities being held in your local area:
FDA Consumer Affairs Officers
Look in the telephone directory under "U.S. Government, Health and Human Services Department, Food and Drug Administration." If it does not appear, contact:

Claudette T. Guilford
Consumer Affairs and Information Staff
FDA, Office of Regional Operations
5600 Fishers Lane, HFC-110, Rockville, MD 20857
(301) 443-4166

NCPIE activities:
Robert Bachman, Executive Director,
National Council on Patient Information and Education
1625 I Street, NW, Suite 1010, Washington, DC 20006
(202) 466-6711

1986

Prescription Drug and Medical Device Patient Education Activities
Status Report - January 1987

OVERVIEW

To assure that prescription drugs and medical devices are used properly, FDA coordinates the development and implementation of major patient education initiatives in the public and private sectors. Since the early 1980s FDA has placed emphasis on patient education programs for prescription drugs and x rays. Activities were also conducted with women's health care devices and hearing aids. These initiatives have been concentrated in three main areas: urging patients to request information; encouraging health professionals to provide information; and monitoring patient education activities.

The prescription drug initiatives began in 1982 with the formation of the National Council on Patient Information and Education (NCPIE). The results of an FDA survey, completed that year, indicated that most patients were not given sufficient information when they received a prescription.

In 1983 FDA and NCPIE launched the "Get the Answers" campaign urging patients to ask their health professionals questions about their prescriptions. The "Get the Answers" message was widely disseminated to consumers and health professional organizations through news releases, advice columns, and multiplier groups. FDA also worked with the Social Security Administration to disseminate the "Get the Answers" message to 36 million social security recipients. In 1983 several private sector organizations (the American Medical Association, the U.S. Pharmacopeia, and the American Association of Retired Persons) developed patient drug leaflet systems for health professionals to use with their patients.

In 1984 FDA conducted a successful "Ask the Doctor about Prescription Drugs" Day in cooperation with the American Academy of Family Physicians and "Call for Action." FDA received the National Association of Consumer Agency Administrators' 1985 "Best Program Award" for this initiative which was conducted in cities across the country. Also in 1984, NCPIE and FDA launched a "Give the Answers" campaign to encourage health professionals to utilize the drug information systems that were available.

In 1985 FDA and other organizations targeted prescription drug patient education efforts to two major groups: the elderly, who take more drugs per capita than do younger individuals in proportion to their representation in the population, and Hispanics, who are often unreached by English language campaigns. Also, NCPIE launched the "Work Site Initiative" which is designed to encourage corporations to disseminate the "Get the Answers" campaign materials to their employees and customers.

In 1986 FDA participated in the first national "Talk About Prescriptions" Month sponsored by NCPIE. Also during 1986 there was increased participation by business, health organizations, and state and local governments in patient education activities.

The x-ray activities began in 1980 when FDA initiated a nationwide public information campaign on diagnostic xrays. The goal of the campaign was, and still is, to activate consumers in their role to maximize the benefits and minimize the risks of diagnostic x rays. The program also promotes building communications between patients and practitioners.

Virtually all FDA offices and staffs have conducted activities in support of FDA's and NCPIE's patient education initiative. A list of contact people appears at the end of the status report.

URGING PATIENTS TO REQUEST INFORMATION

The "Get the Answers" campaign is the primary education program urging patients to ask their health professionals questions about their prescription drugs. FDA, NCPIE, and various other organizations initiated this public communications effort in July 1983. The major component of the campaign is a medical data wallet card that lists the five questions patients should ask when they get a prescription. These questions are:

1. What is the name of the drug and what is it supposed to do?

2. How and when do I take it -- and for how long?

3. What foods, drinks, other medicines, or activities should I avoid while taking this drug?

4. Are there any side effects, and what do I do if they occur?

5. Is there any written information available about the drug?

FDA, NCPIE, and many other organizations helped disseminate the "Get the Answers" message to millions of consumers. For example, FDA worked with the Social Security Administration, the Veterans Administration, and the Consumer Information Center to offer FDA materials on the proper use of medication to over 40 million consumers whom these organizations contact each year.

FDA also has targeted the "Get the Answers" message to specific populations, such as Hispanics and the elderly. There are over 15 million Hispanic consumers in the continental United States. Due to language and cultural differences, a large portion of this population may not be reached by traditional patient education messages.

In order to reach Hispanics FDA has conducted the following initiatives: worked with the National Coalition of Hispanic Health and Human Services Organizations (COSSMHO) to translate the medical data wallet card into Spanish; joined with groups such as the National Hispanic Council on Aging to distribute these cards to Spanish-speaking consumers; utilized a local planning board to develop and implement a demonstration program for Hispanic children in Puerto Rico; and worked with groups such as the Latin Chamber of Commerce to develop and coordinate a Hispanic patient education program in Florida.

In 1986 FDA, NCPIE, and other organizations continued to disseminate the "Get the Answers" message. For example, Gray Drug Fair, Inc. adopted the "Get the Answers" program for a campaign in their 417 stores in 10 states. Also, Citicorp featured "Get the Answers" in its November issue of Choice Comments that is distributed to 830,000 Choice cardholders.

Also in 1986 the American Society of Hospital Pharmacists (ASHP) introduced its major public education campaign, "Go Ahead Ask Your Pharmacist." Their 15-minute videotape focuses on the five "Get the Answers" campaign questions.

State agencies and organizations have also been involved in prescription drug education initiatives. In 1986 the state of South Carolina conducted a campaign utilizing NCPIE's "Ask Your Pharmacist" TV spot and ASHP's "Go Ahead Ask Your Pharmacist" videotapes. These materials were distributed to the state's 12 TV stations. In addition ASHP's video was shown through closed circuit to patients in hospitals across the state. The Iowa Hospital Association Committee on Auxiliaries adopted "Get the Answers" as its 1986 health education campaign.

In addition to continuation of the "Get the Answers" campaign, several new initiatives were conducted to encourage patients to request information about their prescriptions. These initiatives are described below.

I. "Talk About Prescriptions" Month - October 1986

In 1986 FDA participated in the first national "Talk About Prescriptions" Month sponsored by NCPIE. The purpose of the month was to stimulate activity to motivate health professionals to give - and consumers to seek - the information needed for safe and effective medication use. The Commissioner's Health Professional meeting was instrumental in informing health professionals about this effort. FDA Commissioner Frank Young and U.S. Department of Health and Human Services Assistant Secretary for Health, Dr. Robert Windom, joined NCPIE Chairman Paul Rogers at the NCPIE press conference on October 2, 1986 to announce the campaign.

NCPIE developed and distributed a campaign newspaper ("Talk About Prescriptions") that was designed as a do-it-yourself kit containing available materials/resources to support activities planned during October.

FDA distributed the "Talk About Prescriptions" campaign newspaper to newsletter editors, health professional organizations, and several thousand consumers and multiplier organizations. FDA urged these groups to sponsor activities in support of the month, and over 80 groups indicated that they would. National groups, such as Call For Action, and local organizations, such as the Bucks County Area (Pennsylvania) Agency on Aging, conducted special programs and classes, gave speeches, prepared press releases, public service announcements or telephone tapes, or distributed posters and brochures. In addition, the governors from several states signed proclamations to honor National Talk About Prescriptions Month.

Articles promoting the month were included in the October 1986 FDA Consumer and numerous other publications.

II. Elderly Initiatives

The elderly use more prescription drugs per capita than the rest of the population. While those 65 and over constitute about 11 percent of the total population, they take about 25 percent of all drugs dispensed in the United States, both prescription and over the counter. The fact that the elderly must take so many medications increases their chances of experiencing adverse reactions. Therefore, FDA, NCPIE, and other organizations have placed special emphasis on patient education for elderly consumers. Some of the activities directed toward the elderly during 1986 are listed below.

- FDA presented a workshop on the wise use of prescription medicines at the annual convention of the National Council of Senior Citizens (NCSC) held in July 1986. Over 5,000 seniors attended the Miami conference. As a result of FDA outreach, NCSC included an article promoting "Talk About Prescriptions" Month in their October 1986 Retirement newsletter, which has a circulation of 40,000.

- FDA continued to publish materials and conduct meetings across the nation to address issues affecting the elderly population such as drug use in the elderly and health fraud. The October 1986 FDA Consumer magazine included an article on "Protecting the Elderly from Medication Misuse."

- The Healthy Older People Campaign, sponsored by the DHHS Office of Disease Prevention and Health Promotion, featured the safe use of medicines as one of the six areas in which behavior change can make a difference.

- NCPIE received a grant in 1985 from the Commonwealth Fund to develop a mass media campaign designed to improve prescription drug use among the older population. In 1986 the Retirement Research Foundation provided a grant to NCPIE to mount a national public education campaign using the materials that it had developed. The campaign materials will be disseminated nationwide directly to the elderly and appropriate intermediaries. FDA will work with NCPIE on the campaign.

- The American Association of Homes for the Aging (AAHA) included safe use of medicines in its Older Americans Month Project, May 1986. AAHA is a 2,700 member national organization of not-for-profit homes and services for the elderly.

- The National Association of Retail Druggists (NARD) reprinted the "Use Medicines Safely" poster in its September issue of the NARD Journal. This issue also contained the Healthy Older People medication schedule and a list of the program's state contacts. It was distributed to 30,000 pharmacists across the country and attendees at NARD's convention.

- The Pfizer Pharmaceutical Company adopted the Healthy Older People Personal Medications Record, Medications Schedule, and "Use Medicines Safely" skill sheets as part of its "Help Yourself to Good Health" campaign.

III. "Work Site Initiative

To expand the distribution of the "Get the Answers" campaign, NCPIE was awarded a grant from the Exxon Foundation to conduct the "Get the Answers Work Site Initiative". This initiative is designed to encourage corporations to distribute "Get the Answers" materials to their employees, retirees, and customers. This "Work Site Initiative" includes a packet of information with items such as a sample newsletter or magazine article, sample letter to employees, and poster art that have been developed to assist companies in implementing this campaign.

In 1986 NCPIE distributed its initial printing of "Get the Answers" worksite kits and ordered another press run. Kits were distributed to Washington Business Group on Health, Business Roundtable, Business Coalitions Clearinghouse, U.S. Chamber of Commerce, and other groups.

As a result of this initiative, an article on the "Get the Answers" campaign appeared in the July issue of Executive Reports that goes to senior management of all the health insurance companies. The Metropolitan Life Insurance Company Health Action newsletter and Alumni News magazine, which go to over 65,000 people, featured a full page on the "Get the Answers" campaign".

Also the Prudential Insurance Company reproduced and distributed NCPIE patient education materials, including the medical data wallet card, to their active and retired employees. In addition, an issue of AOMA Reports (American Occupational Medical Association) contained an article with ordering information.

IV. X-ray Initiatives

Since 1980 FDA has also promoted improved communications between patients and practitioners regarding the x rays being prescribed for them. FDA pursued this goal by initiating the "X rays: Get the Picture on Protection" campaign. The basic messages of the campaign are to ask the physician or dentist why an x ray is needed, to ask whether a gonad shield can be used, to tell the doctor if you are or think you may be pregnant, to keep a record of x rays taken, and to share this information with the health professional. A key part of this campaign was a wallet card that helped patients keep track of their x rays.

Another x-ray campaign initiated during 1985 concerned reducing radiation exposure during scoliosis radiography. The objectives of this program are to make parents and health professionals aware of the:

- potential health risks (especially to adolescent females) associated with repeated radiation exposure to developing breast tissue;
- recommended methods available to significantly reduce radiation exposure without compromising the quality of the x-ray image; and
- importance of speaking to their doctors about what radiation reduction methods will be used to minimize health risks from excessive exposure when their children are x-rayed.

The FDA published detailed information on scoliosis radiography for both health professionals and consumers. Available for health professionals are a technical report, "Patient Exposure Reduction During Scoliosis Radiography" and a pamphlet, "Reducing Patient Exposure During Scoliosis Radiography"; and for consumers, an FDA Consumer reprint, "When the Spine Curves." Program support materials also included a videotape, slides/script, and a nomadic exhibit appropriate for health professionals; and a tabletop exhibit for consumer audiences. Activities to promote these educational materials have included contact with health professional organizations and journals, newspaper and consumer newsletter editors, popular magazine editors, special interest groups, and education/information clearinghouse editors.

V. Medical Devices Initiatives

In addition to the prescription drug education and x-ray initiatives, FDA has been involved in numerous medical device patient education activities over the past several years. Some of these initiatives were developed in response to a need demonstrated by consumer inquiries to FDA's field and headquarters offices. Other programs were initiated because of recent developments in medical devices, problems with particular devices, and/or new recommended technologies designed to minimize health risks and improve health care.

These medical device patient education programs have included: an education program intended to provide consumers with specific information on the proper use, benefits, and risks associated with women's health care devices; programs to inform consumers about intrauterine contraceptive devices (IUDs); about tampons and toxic shock syndrome (TSS); and a program to inform both health professionals and the general public about the safe and effective use of hearing aids.

Over the past several years, FDA implemented a consumer education program on Women's Health Care Devices. The objective of the program was to provide consumers with specific information on the proper use, benefits, and risks associated with women's health care devices to better enable them to assume an active role in their own health care. The program emphasizes the importance of consulting with physicians about health problems or concerns and to discuss the use of any medical device women may be using or are thinking about using. It also encourages consumers to request patient information materials from their health care providers. Topics covered in the women's health care device program include: menstrual products, birth control devices, diagnostic/monitoring devices, breast reconstruction/augmentation, facial reconstruction, and epilation devices.

Specific consumer education programs containing information on the IUD were implemented. These programs encouraged women to discuss with their physicians the risks and benefits associated with IUD use.

To keep women and physicians apprised of new evidence and scientific findings associated with IUD use, e.g., the high incidence of pelvic inflammatory disease (PID) in IUD wearers, FDA issued, over the years, many messages to the public and to the health care community by way of Drug Bulletin articles, press releases, talk papers, and FDA Consumer articles.

In 1982 FDA implemented a nationwide educational program on tampons and Toxic Shock Syndrome (TSS). In 1985 the Agency developed a poster-format learning unit (endorsed by the American Association for the Advancement of Health Education and the American Academy of Family Physicians) to reach adolescent females. The poster was distributed by FDA and the American College of Obstetricians and Gynecologists to secondary schools, young women's organizations, health professionals, and health administrators/educators. The program focused on the symptoms of TSS, what to do if symptoms occur, and the need to discuss symptoms and the proper use of tampons with physicians.

The Centers for Disease Control also included TSS information in their "Teenage Health Teaching Modules" developed for secondary school health curricula.

In 1986 FDA also initiated consumer education materials on home-use diagnostic devices. A February 1986 FDA Consumer article, "Do-It-Yourself Medical Testing", stressed the need for patients to maintain communication with their health care providers when selecting and using diagnostic testing devices. FDA distributed information concerning home-use diagnostic devices to health writers/editors of popular newspapers and magazines and requested that they use these materials in developing articles. This information also stressed the need for patients to maintain communication with their health care providers.

URGING HEALTH PROFESSIONALS TO PROVIDE INFORMATION

Concurrent with the activities aimed at patients, FDA and many other organizations are conducting a major campaign to encourage health professionals to provide information to their patients. Urging consumers to "Get the Answers" and health professionals to "Give the Answers" is vital to bridge the communications gap - to get both sides to talk to each other.

The NCPIE "Give the Answers" campaign is asking health professionals to take the initiative in giving patients the information they need to use prescription drugs safely and effectively. The initial thrust of this campaign was the distribution of a sourcebook for the professional that provided descriptions, illustrations, and ordering information for a selected set of prescription drug leaflets, booklets, and books appropriate for patient counseling. These sourcebooks were distributed to physicians at an American College of Cardiology meeting and to pharmacists at the annual meeting of the American Pharmaceutical Association.

FDA supported the "Give the Answers" campaign by developing a health professional exhibit program to reach the practicing health professional. The program has been displayed at a number of national health conferences and has been well received by the attendees. FDA also conducted a number of programs related to patient education with health professionals such as a special conference at Howard University and a presentation for the Area Health Education Centers.

The "Give the Answers" campaign was also designed to involve nurses. NCPIE has produced a TV public service announcement encouraging consumers to ask their nurse for information about prescription drugs. The American Nurses' Association, the National League for Nursing, the Nurses' Association of the American College of Obstetricians and Gynecologists, and the Oncology Nursing Society actively promoted the public service announcement in their communities. In addition, many professional nursing journals promoted the availability of the NCPIE booklet entitled, "A Sourcebook for Nurses: Counseling Patients About Their Medicines."

In 1986 the "Give the Answers" print advertisement was featured prominently in the May 1986 Medical Times special issue on patient education. Also Winthrop Breon Laboratories (Sterling Drug) distributed 39,000 "Talk About Prescriptions" posters to physicians and hospital pharmacists through its detail sales force. The FDA Drug Bulletin alerted physicians to "Talk About Prescriptions" Month and the possibility that their patients might ask questions regarding their medicines.

The Oklahoma Pharmaceutical Association designated the week of May 25-31, 1986 as Oklahoma Pharmacy Week, and printed and mailed a poster to over 5000 pharmacists across the state. A cover letter from the Association's Executive Director urged participation in the event, suggested activities, and included an order form for "Give the Answers" campaign materials.

In 1986 the American Pharmaceutical Association and the Pharmaceutical Manufacturers Association launched a major patient compliance campaign. The campaign, aimed at the one third of the population that improperly takes medicines, includes TV and radio PSAs, a film, posters, fliers, and print ads to health professionals. The theme is "Your health is in your hands". This campaign is considered to be ancillary to NCPIE, focusing primarily on how and when to take drugs.

In addition to FDA and NCPIE efforts, many health professional and private sector groups have developed and are continuing to promote specific drug information systems to help health professionals provide prescription drug information to their patients. For example:

The United States Pharmacopeia (USP) produces a comprehensive source of information on drugs in the form of United States Pharmacopeia Dispensing Information (USPDI) and drug specific patient information sheets.

The American Medical Association utilizes the USP data base for its Patient Medication Instruction (PMI) leaflet program. Eighty-two different leaflets are currently available.

The American Academy of Family Physicians is promoting an improved version of its Drug Use Education Tips (DUET) program. The program consists of sets of 300 monograph abstractions printed in loose leaf form so that physicians can photocopy appropriate pages for their patients.

The National Association of Retail Druggists utilizes the USP data base for its Patient Information Leaflets Program -- 33 leaflets covering approximately 200 generic entities are currently available.

The American Dental Association is promoting a series of drug leaflets for those drugs used in dentistry.

Medical Strategies, Inc., in cooperation with USP, is selling a kiosk (Pharmacy Information Center) which will allow customers in a pharmacy, hospital, clinic, or group practice setting to receive via a video terminal information about the drugs that are being prescribed for them.

MONITORING PATIENT EDUCATION ACTIVITIES

FDA and others are continuing to evaluate the effectiveness of patient education programs and are monitoring the attitudes and behavior of consumers and health professionals about patient information. In this regard, FDA has conducted surveys on consumers' attitudes and experiences, and NCPIE and the Pharmaceutical Manufacturers Association have produced directories of drug information programs and resources. Details of the activities follow.

In 1985 FDA conducted a survey of consumers' attitudes and experiences regarding prescription drug information. This survey was a follow-up to a 1982 survey on the same topic and contained an in-depth section on what encourages or discourages questions from consumers to their health professionals.

In 1986 FDA completed a segmentational analysis of data from this 1985 survey. Four types of respondents were identified, based on their methods of obtaining information about their medications.

More than one out of three respondents (34 percent) were classified as "uninformed"; they were unlikely to receive written information about their medications from their doctor or their pharmacist, and appeared unmotivated to seek information from any source. Other groups received counseling from their physicians and pharmacists, or used sources such as reference books, magazines, and friends for drug information. It is the "uninformed" group that the study's authors saw as most in need of motivational messages to learn more about their prescription drugs. "These individuals may not recognize the problems that may occur if drugs are used improperly, nor may they perceive the need for their own vigilance and concern when taking medication."

The survey results suggest that the "Get the Answers" consumer education campaign and the "Give the Answers" professional education campaign are accurately based on some strongly held and documented consumer perceptions. As a result, the campaigns have focused on using appropriate techniques and mechanisms to improve the flow of information between patient and health professional, and urging health professionals to use written information to reinforce medication counseling.

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The Pharmaceutical Manufacturers Association has developed a directory entitled Sources that is designed to inform consumers about health information materials available from member companies. Nearly 400 different sources are listed in this indexed catalogue that covers a broad range of topics including preventive health, understanding disease processes, and specific information about pharmaceutical products. The directory allows consumers to order patient education materials from PMA member companies.

FDA continues to be encouraged by the number and quality of patient education activities undertaken by the various sectors. FDA will continue to provide resources and leadership to foster the patient education initiative.

Office of Consumer Affairs 2/87

For further information on patient education activities you may contact one or more of the following offices:

General information on present and future prescription drug patient education activities.
Kenneth Durham, Deputy Associate Commissioner for Consumer Affairs, HFE-2
FDA, Office of Consumer Affairs
(301) 443-5006

Activities involving health professional associations.
Robert V. Veiga, M.D., Director, Medicine Staff
FDA, Office of Health Affairs, HFY-40
(301) 443-5470

Medical devices patient education activities.
Diana R. Woods, Director, Division of Consumer Affairs
Office of Training and Assistance, HFZ-210
FDA, Center for Devices and Radiological Health
(301) 443-4190

Patient education research.
Louis A. Morris, Ph.D., Acting Director, Division of Drug Advertising and Labeling, HFN-246
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Resource and referral center on patient information and source of patient education materials.
Fran Rowland, Technical Information Assistant
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Patient education activities being held in your local area.
FDA Consumer Affairs Officers
Look in the telephone directory under "U.S. Government, Health and Human Services Department, Food and Drug Administration." If it does not appear, contact:

Consumer Affairs and Information Staff
FDA, Office of Regional Operations
5600 Fishers Lane, HFC-110, Rockville, MD 20857
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NCPIE activities.
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1985

Office of Consumer Affairs

Prescription Drugs Patient Education Activities
Status Report - January 1986

OVERVIEW

In response to the need for effective patient education systems, FDA and the National Council on Patient Information and Education (NCPIE) have coordinated the development and implementation of major patient education initiatives in the public and private sectors during the last four years. These initiatives have been concentrated in three main areas: urging patients to request information; encouraging health professionals to provide information; and monitoring patient education activities.

The initiatives began in 1982 with the formation of NCPIE and the completion of an FDA survey indicating that most patients were not given sufficient information when they received a prescription.

In 1983 FDA and NCPIE launched the "Get the Answers" campaign urging patients to ask their health professionals questions about their prescriptions. The "Get the Answers" message was widely dissmeninated to consumers through news releases, advice columns, and multiplier groups. FDA also worked with the Social Security Administration to disseminate the "Get the Answers" message to 36 million social security recipients. In 1983 several private sector organizations (the American Medical Association, the U.S. Pharmacopeia, and the American Association of Retired Persons) also developed patient drug leaflet systems for health professionals to use with their patients.

In 1984 FDA conducted a successful "Ask the Doctor about Prescription Drugs Day" in cooperation with the American Academy of Family Physicians and "Call for Action." FDA received the National Association of Consumer Agency Administrators' 1985 "Best Program Award" for this initiative which was conducted in cities across the country. Also in 1984, NCPIE launched a "Give the Answers" campaign to encourage health professionals to utilize the drug information systems that were available.

In 1985 FDA and other organizations targeted patient education efforts to two major groups: the elderly, who take more drugs per capita than do younger individuals in proportion to their representation in the population, and Hispanics, who are often unreached by English language campaigns. Also, NCPIE launched the "Work Site Initiative" which is designed to encourage corporations to disseminate the "Get the Answers" campaign materials to their employees and customers.

FDA, NCPIE, and many private sector organizations will continue to work together to increase awareness among patients and health professionals of the importance of communicating information about prescription drugs. FDA will also monitor trends in patient information dissemination in order to lay the groundwork for future patient education activities.

URGING PATIENTS TO REQUEST INFORMATION

The "Get the Answers" campaign is the primary program urging patients to ask their health professionals questions about their prescriptions. FDA, NCPIE, and various private sector organizations initiated this public communications effort in July 1983. The major component of the campaign is a medical data wallet card that lists the five questions patients should ask when they get a prescription. These questions are:

1. What is the name of the drug and what is it supposed to do?
2. How and when do I take it -- and for how long?
3. What foods, drinks, other medicines, or activities should I avoid while taking this drug?
4. Are there any side effects, and what do I do if they occur?
5. Is there any written information available about the drug?

FDA, NCPIE, and many private organizations helped disseminate the "Get the Answers" message to millions of consumers. For example, FDA worked with the Social Security Administration, the Veterans Administration, and the Consumer Information Center to offer FDA materials on the proper use of medication to over 40 million consumers whom these organizations contact each year.

In 1983 FDA produced a news feature to increase consumer awareness and understanding about prescription drugs. This audiovisual was distributed to hospitals and television stations nationwide. It identified the availability of drug information sources and encouraged consumers to talk to their doctor and pharmacist about their medications.

In 1985 several new initiatives were started to encourage patients to request information about their prescriptions. Each is briefly discussed below.

I. Hispanic Initiatives

There are over 15 million Hispanic consumers in the continental United States. A large proportion of Hispanics are isolated by living arrangements (e.g. in inner city barrios) or by their difficulties with the English language. This isolation may limit their access to patient information. Therefore, FDA and other organizations have made special efforts to target patient education activities to Hispanics. These Hispanic initiatives included: translation and distribution of the medical data wallet card in Spanish; developing and implementing a demonstration program for Hispanic children in Puerto Rico; and developing and conducting a Hispanic patient education program in Florida. Descriptions of these Hispanic initiatives follow.

- FDA and the National Coalition of Hispanic Mental Health and Human Services Organizations (COSSMHO) translated the medical data wallet card into Spanish and joined with NCPIE, the American Red Cross, the National Council of La Raza, the National Hispanic Council on Aging, and the National Association of Community Health Centers, Inc. to distribute them to Spanish speaking consumers throughout the country. The objective of this campaign was to have Hispanic patients and health professionals work together to improve the exchange of information about prescription drugs.

  A Spanish language "Get the Answers" print advertisement was also distributed to major Spanish language newspapers and Hispanic service organizations.

- FDA and the University of Colorado's Health Sciences Center developed a demonstration question-asking program, called PROYECTO HEPA, for children in Puerto Rico. PROYECTO HEPA focuses on the following health behaviors: Hablar (talk with the health care provider); Escuchar (listen to the health care provider); Preguntar (ask questions of the health care provider); and Aprender (learn to take care of their health, following decisions made by the health team -- doctor, nurse, parent, and child). The program teaches children how to participate with health care providers during health care visits.

- In October 1985 FDA's Orlando District, the Latin Chamber of Commerce, the Cuban Pharmaceutical Association, and UpFront, Inc. announced a Hispanic patient education program called Proyecto Respuestas (Project Answers). The project is composed of two phases: a continuing education seminar for health professionals and a 24-hour Medication Information System. Spanish speaking consumers can call this Medication Information System for information on prescription and over-the-counter drugs. Phones will be answered by volunteer university students from health related careers. This system will be supplemented by a 30-minute educational videotape on the safe use of medications and other related patient and drug information materials in Spanish.

II. Elderly Initiatives

The elderly use more prescription drugs per capita than the rest of the population. While those 65 and over constitute about 11 percent of the total population, they take about 25 percent of all drugs dispensed in the United States, both prescription and over-the-counter. The fact that the elderly must take so many medications increases their chances of experiencing adverse reactions. Therefore, FDA, NCPIE, and other organizations have placed special emphasis on patient education for elderly consumers. Some of the activities directed toward the elderly during 1985 are listed below.

- FDA and the National Council of Senior Citizens (NCSC) worked together to present the "Get the Answers" message to the Council's Senior Alert Industrious Dedicated Energetic Services (AIDES) program. NCSC currently operates 137 Senior AIDES Projects in 27 states and the District of Columbia.

- FDA worked with project directors in ACTION's Older Americans Volunteer Program to provide information on prescription drugs to grassroots elderly consumers in their respective communities. As part of this effort, the Agency presented a workshop and provided resource packages for ACTION's project directors at their training conference held in 1985.

- FDA organized and presented a session on "Drug Education and the Elderly" for the Gerontological Society of America.

- FDA contracted for the distribution of a column entitled "Safety Sense" to 4000 newspapers nationwide. This column was designed specifically for the elderly patient and provided safety tips on the usage of prescription medicines.

- FDA assisted National Public Radio in producing a documentary program entitled "Senior Citizens: Facing the Prescription Dilemma." FDA experts were interviewed for the program which was aired as part of the "Horizons" series in October.

- NCPIE is also pursuing a patient education program directed at the elderly. NCPIE has been awarded a grant from the Commonwealth Fund of New York to develop a media campaign aimed at improving the use of prescription medications among the elderly. Under this grant, NCPIE developed a priority setting agenda, a communications strategy, and campaign materials which will be tested and then implemented with the assistance of NCPIE members and other organizations.

III. "Work Site Initiative"

To expand the distribution of the "Get the Answers" campaign, NCPIE was awarded a grant from the Exxon Foundation to conduct the "Get the Answers Work Site Initiative". This initiative is designed to encourage corporations to distribute "Get the Answers" materials to their employees, retirees, and customers. This "Work Site Initiative" includes a packet of information with items such as a sample newsletter or magazine article, sample letter to employees, and poster art that have been developed to assist companies in implementing this campaign. This initiative was announced in November 1985 and should be a major focus of FDA and NCPIE activities in 1986.

IV. "National Prescription Medicine Awareness Month"

In November 1985 NCPIE announced that October 1986 will be "National Prescription Medicine Awareness Month". The purpose of this event is to focus national attention on patient education. In addition, it is hoped that widespread media coverage will attract additional organizations to conduct special medication awareness activities. These activities should help facilitate the kind of dialogue between patients and health care professionals that ensures prescription medicines are used appropriately.

ENCOURAGING HEALTH PROFESSIONALS TO PROVIDE INFORMATION

Concurrent with the activities aimed at patients, FDA, NCPIE, and many private sector organizations are conducting a major campaign to encourage health professionals to provide drug information to their patients. Urging consumers to "Get the Answers" and health professionals to "Give the Answers" is vital to bridge the communications gap - to get both sides to talk to each other about medications.

The NCPIE "Give the Answers" campaign is asking health professionals to take the initiative in giving patients the information they need to use prescription drugs safely and effectively. The initial thrust of this campaign was distribution of a sourcebook for the professional that provided descriptions, illustrations, and ordering information for a selected set of prescription drug leaflets, booklets, and books appropriate for patient counseling. These sourcebooks were distributed to physicians at an American College of Cardiology meeting, and to pharmacists at an annual meeting of the American Pharmaceutical Association.

The "Give the Answers" campaign was also designed to involve nurses. On March 1, 1985, NCPIE released a TV public service announcement encouraging consumers to ask their nurse for information about prescription drugs. The 30-second spot was distributed to over 200 television stations in all 50 states.

The American Nurses' Association, the National League for Nursing, the Nurses' Association of the American College of Obstetricians and Gynecologists, and the Oncology Nursing Society joined with NCPIE in 1985 to actively promote the public service announcement in their communities. In addition, many professional nursing journals promoted the availability of the NCPIE booklet entitled, "A Sourcebook for Nurses: Counseling Patients About Their Medicines." The sourcebook provides practical information and resources for nurses regarding patient drug education, and is designed to enhance nurse-patient counseling about prescribed medicines.

In addition to FDA and NCPIE efforts, many health professional organizations have developed and are continuing to promote specific drug information systems to help health professionals provide written drug information to their patients. For example:

The United States Pharmacopeia (USP) produces a comprehensive source of information on drugs in the form of United States Pharmacopeia Dispensing Information (USPDI) and drug specfic patient information sheets.

The American Medical Association utilizes the USP data base for its Patient Medication Instruction (PMI) leaflet program. Eighty-two different leaflets are currently available. In 1986 AMA and the Pharmaceutical Manufacturing Association plan to join in promoting the PMI program through the drug company representatives who personally visit physicians across the country.

The American Academy of Family Physicians introduced an improved version of its Drug Use Education Tips (DUET) program. The program consists of sets of 300 monograph abstractions printed in loose leaf form so that physicians can photocopy appropriate pages for their patients.

The National Association of Retail Druggists utilizes the USP data base for its Patient Information Leaflets Program -- 33 leaflets covering approximately 200 generic entities are currently available.

The American Dental Association has developed a series of drug leaflets for those drugs used in dentistry.

The Michigan Pharmacists Association has developed a "Patient Education Program" that features a newly designed USP Medication Information Sheet that has larger type and is geared for low literacy. In addition to the Medication Information Sheets, patients receive illustrations on how to properly administer ear, eye, nose, and rectal drugs. The program is also being offered to interested health professionals outside of Michigan.

MONITORING PATIENT EDUCATION ACTIVITIES

FDA and NCPIE are continuing to evaluate the effectiveness of patient education programs and are monitoring the attitudes and behavior of consumers and health professionals about patient drug information. In this regard, FDA has conducted surveys on consumers' attitudes and experiences, and NCPIE and the Pharmaceutical Manufacturers Association have produced directories of drug information programs and resources. Details of these activities follow.

In 1985 FDA conducted a survey of consumers' attitudes and experiences regarding prescription drug information. This survey was a follow-up to a 1982 survey on the same topic and contains an in-depth section on what encourages or discourages questions from consumers to their health professionals.

Findings from the survey should provide organizations developing consumer messages greater insight into keys and barriers to useful patient/professional interactions. A preliminary analysis of the survey indicates that elderly people are less likely than younger people to be counseled by either the physician or the pharmacist regarding medications prescribed for them. Overall, one-third of the elderly are not counseled by either of these health professionals, compared to one-fourth of the rest of the population.

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The survey also identified a tendency for the elderly to be less likely than younger consumers to receive warning information, such as the potential for adverse reactions or interactions with other medications, from either the physician or the pharmacist. While the elderly are less likely to receive written information at the pharmacy, they are slightly more likely to receive some written materials at the doctor's office.

In addition, elderly consumers have different perceptions than do younger persons about the need to ask questions about prescription drugs. The elderly are more more likely to believe that trust in the doctor negates the need to ask questions. However, both younger and older patients considered it a good idea to write down questions before an appointment with a physician.

The survey response suggests that the "Get the Answers" consumer education campaign and the "Give the Answers" professional education campaign are accurately based on some strongly held and documented consumer perceptions. As a result, the campaigns have focused on using appropriate techniques and mechanisms to improve the flow of information between patient and health professional, and messages to health professionals urging them to use written information to reinforce medication counseling.

In 1986 FDA plans to conduct a segmentational analysis of data from this survey. This analysis will focus on the drug information needs of different groups, such as the elderly, and help further target education efforts based on these findings.

At its 4th Annual Meeting held in November 1985, NCPIE released a Directory of Prescription Drug Information and Education Programs and Resources. This directory, done in cooperation with FDA, is intended to assist organizations and health professionals in the development of new prescription drug information and education programs/materials appropriate to their settings and audiences. It lists 184 programs being conducted by a wide range of organizations such as the Arthritis Foundation, the American Association of Retired Persons, National Cancer Institute, various pharmaceutical companies, drug chains, and pharmacy schools. It is anticipated that the directory will be updated at least every two years.

The Pharmaceutical Manufacturers Association has developed a directory entitled Sources that is designed to inform consumers about health information materials available from member companies. Nearly 400 different sources are listed in this indexed catalogue that covers a broad range of topics including preventive health, understanding disease processes, and specific information about pharmaceutical products. The directory allows consumers to order patient education materials from PMA member companies.

Page 9 - Prescription Drugs Patient Education Activities

FDA continues to be encouraged by the number and quality of patient education activities undertaken by the various sectors. Efforts to increase awareness must be ongoing and repetitive in order to achieve success. FDA will continue to provide resources and leadership to foster the patient education initiative.

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Patient Education Activities
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In response to the need for effective patient education systems, FDA has coordinated the development and implementation of major patient education initiatives in the public and private sectors during the last three years.

The major accomplishments in 1982 were the formation of the National Council on Patient Information and Education (NCPIE) and the completion of an FDA survey indicating that most patients were not given sufficient information when they received a prescription.

In 1983 FDA and NCPIE launched the "Get the Answers" campaign urging patients to ask their health professionals questions about their prescriptions. The "Get the Answers" message was widely disseminated to consumers through news releases, advice columns, and multiplier groups. FDA also worked with the Social Security Administration to disseminate the "Get the Answers" message to 36 million social security recipients. In 1983 several private sector organizations (AMA, USP, AARP) also developed patient drug leaflet systems for health professionals to use with their patients.

In 1984 FDA conducted the successful "Ask the Doctor about Prescription Drugs Day" and NCPIE launched a "Give the Answers" campaign to encourage health professionals to utilize the drug information systems that are now available.

FDA, the National Council on Patient Information and Education, and many private sector organizations will continue to work together to increase awareness among patients and health professionals of the importance of communicating information about prescription drugs, especially to the elderly who are the main users of prescription drugs. The Agency will also monitor trends in patient information dissemination in order to lay the groundwork for future patient education activities.

Urging Patients to Request Information

FDA, NCPIE, and various private sector organizations initiated a major public communications effort called the "Get the Answers" campaign in July 1983 to urge patients to request information about their prescriptions. The major component of the campaign is a medical data wallet card that lists the five questions patients should ask when they get a prescription. FDA, NCPIE, and many private companies have reprinted millions of wallet cards for their customers and employees.

NCPIE now plans to involve several major corporations in its "Get the Answers" campaign by asking them to:

a. Communicate to their employees the importance of asking basic questions about their prescription medicines by displaying posters and cafeteria table tent cards, by including articles in internal newsletters, and by distributing wallet cards and brochures.

b. Reprint and distribute wallet cards and/or brochures as a public service to customers.

An invitation to participate will be sent to appropriate contacts in major corporations. Press releases will announce the participating companies and serve to stimulate increased corporate participation.

In recent months FDA and NCPIE have also laid the groundwork for communicating the "Get the Answers" message to two important target audiences: Hispanics and the elderly.

FDA, NCPIE, and the Coalition of Spanish Speaking Mental Health Organizations (COSSMHO) have worked together to translate the wallet cards into Spanish. As a result of the collaboration, approximately a quarter million wallet cards will be distributed to Hispanic audiences over the next year.

FDA is exploring possible joint programs with organizations serving the elderly to help disseminate the "Get the Answers" message. NCPIE will also develop a specific campaign to reach the elderly. NCPIE recently received a $75,000 grant from the Commonwealth Fund to design a campaign strategy, identify subgroups within the target population, and develop and field-test appropriate materials.

Encouraging Health Professionals to Provide Information

Concurrent with the activities aimed at patients, FDA, NCPIE, and many private sector organizations are conducting a major campaign to encourage health professionals to provide drug information to their patients.

NCPIE has recently launched a new campaign which calls on physicians and other health care professionals to give the answers to patients and consumers. This "Give the Answers" campaign urges health professionals to answer the five questions when counseling patients even if the patients don't take the initiative to ask.

NCPIE will stimulate editorial comment in professional journals, rovide a "Give the Answers" slide show to professional ocieties, and widely disseminate its materials through health professional organizations and at health professional meetings across the country.

In addition to FDA and NCPIE efforts, many health professional organizations have developed and are continuing to promote specific drug information systems for patients. For example:

United States Pharmacopeia - The USP System of Drug Use Information now covers nearly all prescription and nonprescription medicines used in the United States. For each medicine, one monograph provides the relevant information for the health care provider and a second monograph provides information in lay language for the patient. The USP has been especially active in promoting their materials to state pharmaceutical associations. Leaflet programs have been adopted in Washington, Louisiana, Montana, Missouri, Colorado, Texas, and Michigan.

American Medical Association - The AMA utilizes the USP data base for its Patient Medication Instruction (PMI) leaflet program. Eighty-two different leaflets are currently available.

American Academy of Family Physicians - AAFP's new version of its Drug Use Education Tips (DUET) program has experienced increased physician participation. The program consists of sets of 300 monograph abstractions printed in loose leaf form. The first printing has been sold out and over 1200 orders are awaiting a second printing.

National Association of Retail Druggists - NARD utilizes the USP data base for its Patient Information Leaflets (PILs), and 33 leaflets covering approximately 200 generic entities are currently available.

American Dental Association - ADA has recently developed a series of drug leaflets for those drugs used in dentistry.

Michigan Pharmacists Association - This organization's leaflet program was announced during a Press Conference on October 10, 1984. The Michigan "Patient Education Program" (PEP) features a newly designed USP Medication Information Sheet that is geared for low-literacy and has larger type. In addition to the Medication Information Sheets, patients will receive illustrations on how to properly administer ear, eye, nose, and rectal drugs. The program will also be offered to interested health professionals outside of Michigan.

Monitoring Patient Education Activities

FDA and NCPIE are continuing to evaluate the effectiveness of patient education programs and are monitoring the attitudes and behavior of consumers and health professionals about patient drug information. An FDA survey of consumers was conducted two years ago to collect baseline data about the information consumers were receiving from their health professionals. A new FDA consumer survey is now being conducted to help those interested in patient education develop more effective programs. The results of this second survey are expected in early spring 1985.

NCPIE also plans to survey its members and request descriptions of their patient drug information resources, their patient drug information research, and their education programs. These descriptions will be organized in a standard format listing the activity and the contact person for publication and distribution at NCPIE's 4th Annual Meeting. Currently, there is no listing of patient drug information resources, research, and programs. The NCPIE directory will be available for NCPIE members as well as for distribution to members of Congress and appropriate Federal agencies. It will be designed to answer inquiries about the progress and success of the voluntary approach to prescription drug information and education.

The patient education initiative has reached a crucial phase in its development. When the initiative was first implemented, there were no readily available specific drug leaflet programs; leaflet systems are now available. The success of the initiative will be indicated by increased awareness and usage by patients and health providers. Efforts to increase awareness must be ongoing and repetitive in order to achieve success. FDA will continue to provide resources and leadership in fostering the patient education initiative.

1983

Status Report on Patient Education Activities

March 1984

FDA Initiatives

Over the last year, the Agency has undertaken many initiatives to communicate patient information to consumers. Some of the major efforts include the following:

- FDA and the Social Security Administration worked together to mail a patient education insert to 36 million Social Security recipients. The insert encouraged patients to ask their doctors for drug information and offered a free brochure on drugs from the Consumer Information Center in Pueblo, Colorado. The mailing received extensive coverage in both newspapers and professional journals, and more than 355,350 brochures were requested by the public.
- 480,000 copies of a "Go Ahead, Ask Your Doctor or Pharmacist" brochure were placed in 4,800 high-volume supermarkets across the nation in July and August. The brochure emphasized the information patients should know about their medications.
- The August issue of the FDA *Drug Bulletin* contained an article announcing the mailing of the Social Security insert and describing the patient education efforts undertaken by the government and private sectors. The *Bulletin* is circulated to over one million health professionals.
- FDA mailed a series of "Go Ahead, Ask Your Doctor" print ads to 9,000 daily and weekly newspapers and general circulation magazines. These ads stress the five questions patients should ask about their medications.
- FDA offered a 3-minute patient education videotape to 4,500 hospitals. To date, 1,427 hospitals have ordered the videotape, representing a 31 percent response rate.
- FDA contacted the Health Resources and Services Administration, the Department of Defense, and the Veterans Administration to solicit their cooperation in encouraging government-affiliated physicians and pharmacists to dispense drug information leaflets.

National Council on Patient Information and Education

The National Council on Patient Information and Education (NCPIE) was formed in October 1982 in response to the need to improve communications between patients and health professionals about prescription drugs. The Council has grown from its 23 founding members to 195 active member organizations, including health care providers, consumers, industry, and others.

The Council's 1983 objectives focused on raising the awareness of both patients and health professionals about the importance of knowing basic facts about prescription medications and outlining actions both can take to improve communication. The Council accomplished its goals through a national "Get the Answers" campaign, an extensive mass media effort, and public presentations and testimony to interested audiences.

The "Get the Answers" campaign, launched in July 1983, encourages consumers to ask their health professionals five basic questions about every drug they are prescribed, and encourages health professionals to meet patient information needs. The wallet cards developed by NCPIE list the five questions patients should ask and provide space to write information on drugs and personal medical history. The "Get the Answers" kit, which was distributed to member organizations and their state and local affiliates, provides health professionals with a variety of educational and promotional materials that can be used to promote patient/health professional communication. Response to the campaign, which will continue into 1984, has been very good, with local groups ordering over 16,000 kits and 500,000 wallet cards, brochures, and posters in the first three months of the program.

FDA is actively supporting the "Get the Answers" campaign by encouraging organizations to reprint and distribute the NCPIE medical data wallet cards. Agency Consumer Affairs Officers throughout the country are appealing to utility companies and regional food and department stores to distribute the cards. As of this date, these companies have indicated that they will reprint over 1.5 million wallet cards and will disseminate an additional 500,000 cards that will be provided by FDA.

NCPIE's mass media efforts included distribution of three public service announcements (encouraging patients to ask questions about their drugs) to over 170 local television stations across the country.

NCPIE's next major communication campaign, will be directed at health professionals. It will be entitled, "Give the Answers" to complement the "Get the Answers" campaign.

Private Sector Initiatives

Over the last year, many health professional organizations have continued their support and involvement in the patient education initiative. Following are some of the significant contributions:

- The American Medical Association (AMA) prepared 60 Patient Medication Instructions (PMIs) and will add PMIs on 20 new drug classes every six months. AMA also conducted a telephone survey of 1,015 physicians which revealed that even though only a small percentage of physicians have ordered the pads, of those who have ordered indicated that they will continue their use. In light of this finding, AMA will continue to encourage trial usage of PMIs by physicians.
- The National Association of Retail Druggists (NARD) is providing patient information leaflets for nine specific drugs and 23 drug families to NARD members. In addition to the leaflets, NARD will furnish a file box and promotional material including countercards, posters, leaflets, and public service announcements.
- The United States Pharmacopeia (USP) is encouraging large institutions and pharmacy associations to distribute patient education leaflets prepared by USP. USP has also developed drug information leaflets in Spanish for 50 widely-used drugs and, in concert with Montefiore Hospital in New York, has developed a prototype bilingual drug information leaflet in English and Spanish.
- The American Association of Retired Persons (AARP) Pharmacy Service prepared 50 Patient Advisory Leaflets discussing over 160 drugs. The leaflets, which contain large print and bold illustrations, are included with prescriptions filled by the AARP Mail Order Pharmacy Service.
- Numerous articles, publicizing patient education initiatives in both the public and private sectors, have appeared in professional journals. Patient education articles, written by individuals actively involved in promoting patient education, have appeared in Patient Care, American Pharmacy, American Journal of Public Health, Postgraduate Medicine, Pharmacy Journal, and AARP Pharmacy System Evaluation.

Monitoring Patient Information and Education Activities

To assist in the development and implementation of effective patient education programs, FDA is monitoring the attitudes and behavior of consumers and health professionals about patient drug information. Surveys have been conducted to collect baseline data and will be repeated periodically to determine changes and trends in drug information dissemination.

- A survey of 1,104 consumers, conducted by Chilton, Inc., showed that only 6 percent of consumers were given written information in their doctor's office, and 15 percent received written material at the pharmacy. Twenty-two percent of patients remembered receiving oral information on how much medicine to take, and 7 percent reported being told about side effects by either the physician or pharmacist. Fewer than 5 percent of consumers asked their health professionals for information about their drugs.

- A survey was conducted for FDA by Louis Harris and Associates to measure the attitudes and reported behavior of physicians and pharmacists regarding patient drug information. The surveys, which polled 501 family physicians and 500 community pharmacists about medication prescribing habits, revealed a wide gap between what health professionals think they are communicating to patients and what information patients say they are receiving.

  According to the survey, doctors believe most of their patients are getting adequate information about their prescribed medications, and one-third of the physicians surveyed report they give their patients supplemental written material. Pharmacists reported that they usually talk to their customers about new prescriptions, and over two-thirds report that they hand out written materials.

  Both doctors and pharmacists agree that patients do not ask enough questions. Because so few questions are asked, doctors feel patients are satisfied with the information they receive; pharmacists report they are only asked questions about one out of three prescriptions they fill.

- The American Association of Retired Persons conducted a survey of 2,400 members who receive drug information leaflets with their prescriptions filled by the AARP mail order prescription service. The survey revealed that 95 percent of those who received prescription drug information read it, with 76 percent retaining the leaflet for later referral. Over 90 percent said they found the information useful and almost 70 percent reported they learned new information from the leaflet. Forty-two percent reported that the leaflet made them feel better about taking their medicines, while 56 percent said the leaflet had not changed their opinion about taking their medicines.

The CBS Broadcasting Company conducted a survey of consumers to determine their knowledge and need for information about prescription drugs. The study concluded that people think it is highly important and have a great need for information about prescription drugs. In particular they want more information about safety and efficacy (side effects, interactions, etc.), and proper home use (dosage, when to take, etc.).

Future Initiatives

FDA's goals for the coming year are two-fold: to continue to urge patients to ask questions when they get a prescription; and to motivate health professionals to provide drug information to their patients when they prescribe or dispense a drug. To achieve these goals, the Agency is working on several initiatives which are highlighted below:

- FDA is working with the American Academy of Family Physicians, and Call for Action, a non-profit information and referral service in the U.S., to establish a national "Ask the Expert" day for prescription medicines. To date, such programs have used attorneys, accountants, and other experts to respond to telephone calls off the air at designated times to provide information and referrals. The 24 participating radio and TV stations provide free air time to advertise the "Ask the Expert" program and reach 40 million people. An "Ask the Expert" day, using health professionals to answer calls on prescription medications is tentatively scheduled for September 19. This program will be widely publicized during August and September.

- FDA, the National Medical Association, and Howard University plan to sponsor a patient education conference on June 9, 1984. The conference will provide health professionals in the Washington, D.C.

area with information on the tools that are available to help them implement patient education programs. It is hoped that this conference will become a model that can be replicated in other parts of the country.

- FDA is developing a 15-minute consumer film on patient education which will be distributed to schools and community groups.
- FDA will distribute a public service print advertisement to all health professional journals and magazines urging them to communicate drug information to their patients. A patient education exhibit is also being scheduled for a number of health professional meetings.
- FDA, the Cuban Pharmacy Association and Up Front, Inc. conducted a one-day workshop to address basic issues and needs of the Hispanic community concerning patient education. The pilot was conducted in the Miami area for health professionals.
- FDA is exploring the feasibility of implementing a question-asking program for Hispanic communities in Puerto Rico which would increase consumer awareness of drug use and stimulate dialogue between consumers and health care providers. The program would be modeled after the University of Colorado's Question-Asking Program for Children. It teaches young people how to talk to, ask questions of, listen and learn from health professionals, and teaches health care providers to listen to, and educate and motivate consumers to share responsibility for their health care.
- FDA plans to conduct another consumer survey late in 1984 to fine tune patient education efforts and evaluate the success of the programs so far. The National Council on Patient Information and Education will again be asked to help design the survey.

SUMMARY

The Agency is continuing to monitor various patient education programs. Results of the consumer, physician, and pharmacist surveys indicate the need for increased dialogue between patients and health professionals. The AARP survey reveals that patients who receive written prescription drug information find it useful. In addition, the results of a recent Roper survey indicate that consumers feel there is a need for more information about prescription drugs; they think brochures, toll free information numbers, and radio, TV, and newspaper stories would be effective means for relaying this information.

The FDA, NCPIE, and private sector organizations have worked in the last year to meet these needs and will continue to focus their efforts to provide effective patient education programs for patients and health professionals. Since the formation of FDA's Committee on Patient Education in 1982, much progress has been made in the area of patient education. The major problem still to be addressed, is convincing health professionals to better communicate drug information to their patients.

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LOUISE M SLAUGHTER, NEW YORK
HARLEY O STAGGERS, JR., WEST VIRGINIA
FRANK PALLONE, JR., NEW JERSEY
JOLENE UNSOELD, WASHINGTON
EDWARD R. ROYBAL, CALIFORNIA
(EX OFFICIO)

JOHN P. OLINGER
STAFF DIRECTOR
(202) 226-3348

U.S. House of Representatives
SELECT COMMITTEE ON AGING
SUBCOMMITTEE ON HUMAN SERVICES
811 House Office Building Annex 1
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NATALIE CANNON
MINORITY STAFF DIRECTOR
(202) 226-3349

June 15, 1989

Dr. Frank E. Young
Commissioner
Food and Drug Administration
Room 14-71 Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

Thank you for your letter of June 1 in which you supplied a partial response to my letter of May 15 requesting that several items be sent for inclusion in the official hearing record from the Subcommittee hearing held on April 19 on Drug Misuse Among the Elderly.

While I appreciate your cooperation, I am disappointed that a more complete response was not sent. As you are aware, this is a matter of great importance not only to the Subcommittee on Human Services, but also to millions of senior citizens who must rely on prescription drugs in order to live comfortably and independently.

It is my hope that the remaining material that I have requested will be supplied in the very near future. In addition, while I understand the guideline for premarket clinical testing of drugs on the elderly is being circulated internally within FDA for review, I would like to urge its expedient completion within the six months indicated at the April 19 hearing.

I look forward to hearing from you soon.

With best wishes, I am

Sincerely,

THOMAS J. DOWNEY
Chairman

TJD:mb

AP3

MSS
MEDICAL SUPPORT SYSTEMS
6660 Busch Boulevard, Columbus, Ohio 43229 614/846-4111
1-800-822-4976 • FAX: 614/431-3640

April 28, 1989

Congressman Tom Downey
811 House Annex #1
Washington, D.C. 20515

ATTN: Select Committee on Aging
Sub-Committee on Human Services

Congressman Downey:

The attached information is presented as post hearing written testimony on the subject of drug misuse among the elderly, that hearing being held in Washington, April 19, 1989.

I believe that our presented text will strongly corroborate testimony and evidence submitted at the hearing and will assist your efforts in expediting the review and evaluation of viable solutions to the national awareness and concern of mismedication of the elderly.

I have also enclosed information on our company for your review. Please contact me with any questions you may have regarding the enclosed. Thank you for your consideration.

Sincerely,

Michael H. Anderson
President & CEO

MHA/mas

cc: file

encl

"PHARMACOKINETIC DRUG DOSING"

Presented as Post Hearing Written Testimony To

THE HOUSE AGING COMMITTEE HEARING
on
Drug Misuse Among The Elderly And
Its Impact On Community Based Care

April 19, 1989
Washington, DC

Submitted By:

Medical Support Systems, Inc.
6660 Busch Boulevard
Columbus, OH 43229

The enclosed documentation and supportive evidence is presented as post hearing written testimony to The House Aging Committee. The information relates to the widespread problem of mismedication among older adults and the positive clinical and financial impact a Pharmacokinetic Drug Dosing Program would have in combating this problem.

Pharmacokinetics, by basic definition. is a drug dosing science that accurately predicts serum drug levels by analyzing how drugs are absorbed, distributed, metabolized, and excreted by the body. Utilizing clinically proven mathematical and scientific principles, pharmacokinetic drug dosing provides an objective, individualized view of drug therapy and its effectiveness.

Unlike a serum drug level which, like a "snapshot", indicates a patient's therapeutic response at the time the level was drawn, pharmacokinetics is a "motion picture" of therapeutic response and indicates the effectiveness of therapy throughout an entire dosing interval.

All medications have a pharmacokinetic profile. However, certain drug classes are used extensively for long-term therapy to treat chronic diagnoses typically found in the elderly. Additionally, these same drug classes possess certain biopharmaceutical characteristics that make them more conducive to pharmacokinetic drug dosing. These drug classes and their respective medications are: CARDIAC - digoxin, disopyramide, procainamide, and quinidine; RESPIRATORY - theophylline; ANTICONVULSANTS - carbamazepine, phenobarbital, phenytoin, valproic acid, and ethosuximide; ANTIMANIA - lithium; ANTICOAGULANTS - heparin, warfarin, and protamine, and finally; ANTIBIOTICS - gentamicin, tobramycin, kanamycin, amikacin, netilmicin, and vancomycin.

These drug classes have a narrow therapeutic range as defined by parameters which indicate sub-therapeutic, therapeutic, and toxic serum drug levels (See Figure 1). Furthermore, the desired therapeutic patient response is more closely related to plasma drug concentration than to standard dosing. This is significant because the plasma concentration necessary to achieve a therapeutic benefit may occur very near the toxic level. Finally, standard doses of these drugs cannot be established due to the wide variability in interpatient serum levels when administered the same dosage amount.

Medical Support Systems, Inc. is convinced from professional experience that the above referenced characteristics and dosing complexities of these medication that are widely used to treat the elderly contribute significantly to the national problem of mismedication among the elderly.

```
      TEMAZEPAM                              PHENOBARBITAL

s 250 |                                s 250 |
e 225 |---------------THER MAX         e     |
r 200 |                                r 200 |
u     |                                u     |
m 150 |  therapeutic                   m 150 |
      |                                      |
c 100 |---------------THER MIN         c 100 |
o  50 |                                o     |
n     |                                n  40 |---------------THER MAX
c     |                                c     |  therapeutic
      |                                   20 |---------------THER MIN
    0 |______________________             0 |_______________________
              time                                  time
```

(Figure 1)

The accuracy of pharmacokinetic drug dosing has been demonstrated to be over 90%. (1) Clinically developed mathematical models have been proven to be extremely effective in predicting drug serum concentrations when certain patient specific data is provided (i.e. age, height, weight, serum creatinine, albumin, diagnosis, concomitant medications, drug serum levels, etc.) (2)

The viable medium in coupling patient specific information with drug-specific characteristics to optimize drug therapy is pharmacokinetic drug dosing computer software. These computer programs offer accurate and timely analysis necessary to determine proper drug dosing. Important benefits of computer assisted pharmacokinetic drug dosing are: optimization of dose to insure patient receives a therapeutic benefit 24 hours a day for the extent of the regimen; identification of sub-therapeutic drug levels to provide the clinician with a sound foundation to discontinue a drug, or increase the dose to more effectively treat the disease; decreased risk for drug related side effects due to inaccurate dosing, and; simplification of the dosage regimen to reduce medication costs, continue therapeutic benefit, and enhance patient compliance. All of these important benefits result in improved patient care.

In 1985, 243,000 hospital admissions of older adults were for treatment of adverse drug reactions. (3) Additionally, 51% of drug related deaths were elderly Americans who comprise only 17% of the population. (3) Many of these deaths were attributed to physicians prescribing drug regimens noted to be suboptimal in older adults. These factors substantiate the results of mismedication among the elderly and why this situation is labeled by some as "the nation's other drug problem."(4)

Through pharmacokinetic drug dosing, a patient's rehabilitation and response potential may be significantly enhanced as illustrated by numerous clinical studies. (5)(6) Additionally, accurate drug dosing dramatically decreases the risk of adverse drug reactions, thereby saving health care costs and reducing the need for emergency or extended medical intervention (i.e. hospital admission due to uncontrolled seizure activity, adverse drug reaction, or extended hospital stay from ineffective antibiotic therapy). (7)

Since 1987, Medical Support Systems, Inc. has been utilizing pharmacokinetic drug dosing computer software to enhance patient drug therapy in acute and long-term care environments. In January, 1989, our company compiled the results of 1905 randomly selected drug regimens that were analyzed pharmacokinetically. Fully 64% of the drug levels were not optimally therapeutic. 15% were toxic and remaining 49% of the patients indicated a sub-therapeutic response to their prescribed regimens. (8)

In February, 1989, Medical Support Systems, Inc. conducted a pharmacokinetic retrospective study for a large metropolitan hospital in Ohio. The hospital randomly selected 25 patients for pharmacokinetic evaluation of their antibiotic therapy. The results showed that 28% of the patients were toxic, 56% were sub-therapeutic, and 16% were not evaluated due to lack of proper information. These results support the critical importance of pharmacokinetic drug dosing as 100% of those evaluated were not within the therapeutic range. (9)

The same retrospective study also demonstrated that 83% of the hospital's conventional laboratory analyses for these patients yielded no useful information. The cost of these erroneous lab results was estimated to be $3086.10. (9) Furthermore, in a cost benefit analysis prepared for this hospital, Medical Support Systems, Inc. projected substantial annual cost savings for Medicare and Medicaid patients whose drug therapy could be stabilized more quickly utilizing pharmacokinetics, and could therefore be discharged from the hospital up to 30% sooner.

It has been proven that physicians do not accurately prescribe for older persons. Much of this mismedication is due to a lack of knowledge in treating geriatric populations. (3) However, this fact does create a significant opportunity to utilize pharmacokinetics to improve the quality of care provided to the elderly as well as the general public. The Catastrophic Health Bill specifically requires a Drug Utilization Review (DUR) Program that will improve the quality of drug therapy for the elderly.

In response to this requirement, pharmacokinetic drug dosing can be an integral component of DUR and will be particularly meaningful because it is used both at the time of original dosing and to periodically monitor drug levels during therapy. As an analytical tool, pharmacokinetics is a method by which adjustments in drug regimens become obvious. Physicians can clearly interpret graphically illustrated computer generated reports and feel confident that drug dosing is more solidly based on objective data. This is especially important in elderly patients who often cannot or do not discuss with their physician any adverse effects mismedication may be causing.

163,000 of our nation's elderly experience serious mental impairment caused by drugs. This is know to lead to the "illness medication spiral" where mismedication produces side effects that mimic illness. This results in the introduction of additional drugs to treat a perceived newfound symptomology. (10) The tragic cost of mismedication in human terms is incalculable. However, the financial impact of this national problem has been estimated at over $7 billion annually. (11)

Knowing all of this, it is not surprising to find that in a recent drug dosing examination, 70% of the physicians tested failed to pass. (12)

In addition to physicians, pharmacists and pharmaceutical manufacturers will significantly benefit from pharmacokinetics. Pharmacists gain more knowledge about optimizing drug therapy. Perhaps more importantly, pharmaceutical manufacturers can use data gathered from pharmacokinetic analysis of elderly patients to gain a better understanding of drug therapy in a geriatric population. Because pharmacokinetics utilizes patient specific data (i.e. age, height, weight, disease states, renal and hepatic functions, concomitant medications, drug serum levels, etc.), a plethora of information can be obtained, reviewed, and analyzed in researching drug response in the elderly. Currently, the testing of new drugs by manufacturers in geriatric populations is seriously lacking. This is a sad fact because 80% of the population over the age of 65 are diagnosed with chronic diseases that require long-term drug therapy. (3)

Pharmacokinetics is a proven, well documented science enabling physicians, pharmacists, pharmaceutical manufacturers, and researchers to attack the growing problem of mismedication that is clearly evident in today's health care system. Ignorance and lethargy are no long viable excuses for the tragic human and financial burden suffered from inaccurate drug dosing. The implementation of pharmacokinetic drug dosing in health care sectors can insure that goals of improved drug therapy, utilization, and enhanced quality of care are attained in a cost efficient manner.

Medical Support Systems, Inc. is dedicated to advancing the application of pharmacokinetic drug dosing. Acute care and long-term care settings lend themselves especially well to pharmacokinetic drug dosing.

In hospitals, patient drug therapy can be improved through the use of computer-based pharmacokinetics. Software programs are clinically proven and can be operated by members of the pharmacy or medical staff resulting in a service that is provided 24 hours a day, seven days a week.

In nursing home facilities, consultant pharmacists currently provide drug utilization reviews on a monthly basis. These same professionals can easily gather patient specific information for pharmacokinetic analysis performed at an off-site location. Currently, Medical Support Systems, Inc. provides such a service in long-term care with a 48 hour turnaround time. Our protocol recommends that patients on qualifying medications are pharmacokinetically monitored semiannually.

Medical Support Systems, Inc. hopes that this information presented as post hearing testimony will enlighten The House Aging Committee and the governmental health care system of companies and proven clinical methodologies which are available today to address "our nation's other drug problem".

Thank you for your consideration of this testimony.

Sincerely,

Michael H. Anderson
President & Chief Executive Officer

MHA/mas

REFERENCES

1. Robinson JD. "Pharmacokinetics service for ambulatory patients". American Journal for Hospital Pharmacy. 1981: 38:1713-1716.

2. Robinson JD et al. "Introduction to therapeutic drug monitoring and pharmacokinetics". A Textbook for the Clinical Application of Therapeutic Drug Monitoring. 1986: 1-30. Abbott Laboratories Diagnostics Division.

3. Kusserow RP, Inspector General. "Medicare Drug Utilization Review". Control #OAI-01-88-00980. January, 1989.

4. Smyer M et al. "Reducing the risk of prescription drug interactions and estimating risk prevalence of prescription drug interactions in Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) Program". Final report submitted to the Andrus Foundation of AARP. December, 1987:3-4.

5. Zaske ZE et al. "Gentamicin pharmacokinetics in 1640 patients: method for control of serum concentrations". Antimicrobial Agents and Chemotherapy. March, 1982:407-411.

6. Mungall D et al. "Individualizing theophylline therapy: the impact of clinical pharmacokinetics on patient outcomes". Therapeutic Drug Monitoring. 1983:5:95-101.

7. Hurford BS et al. "Needs analysis of a pharmacokinetic dosing service". A Doctor of Pharmacy Thesis. 1-8. University of Cincinnati.

8. Medical Support Systems, Inc., Columbus, OH. "A pharmacokinetics evaluation of 1905 drug regimens". January, 1989.

9. Medical Support Systems, Inc., Columbus, OH. "A pharmacokinetics retrospective study for a large metropolitan hospital in Ohio". February, 1989.

10. Carruthers SG. "Clinical pharmacology of aging". Fundamentals of Geriatric Medicine. 1983. Raven Press.

11. Testimony of Helene Lipton, Ph.D., Associate Professor, Division of Chemical Pharmacy, School of Pharmacy, and Senior Research Associate, Institute for Health Policy Studies, School of Medicine, University of California, San Francisco, before the Senate Special Committee on Aging. July, 1987.

12. Ferry ME et al. "Physicians' knowledge of prescribing for the elderly". Journal of the American Geriatrics Society. 1985:33:616.

MEDICAL SUPPORT SYSTEMS, INC.
6660 Busch Boulevard
Columbus, Ohio 43229
(800) 822-4976

[PHARMACOKINETIC DRUG DOSING SERVICES]

Disease states, multiple medications, decreased organ function, and other factors affect the absorption, distribution, metabolism, and excretion of drugs and can complicate desired therapeutic goals of drug regimens. Therefore, accurate drug dosing is critical in ensuring optimum care.

At Medical Support Systems, Inc. (MSS), our goal is to improve the quality of drug and patient care offered in today's health care setting by providing *Pharmacokinetic Drug Dosing*. Pharmacokinetics yields valuable and needed information to accurately dose certain classes of drugs such as:

CARDIAC - RESPIRATORY - ANTIMANIA
ANTICOAGULANTS - ANTICONVULSANTS - ANTIBIOTICS

These drug classes are candidates for pharmacokinetic analysis because:

- *patient response depends upon plasma drug concentration, not drug dosage;*
- *a narrow range exists between the minimum therapeutic serum concentration and that toxic level which is likely to produce adverse effects, and;*
- *among different patients, a wide variability in serum concentrations will occur from identical drug regimens.*

A computer-assisted pharmacokinetic analysis results from combining the pharmacokinetic profile of the drug with the medical profile of the patient and determines the optimal dosage quickly and cost-effectively.

MSS is an Exclusive Licensee of pharmacokinetic drug dosing software and services developed by Data Med Clinical Support Services, Inc. Since 1987, we have been committed to advancing the application of this patient management technology. Our clientele include physicians, acute and long-term care facilities, institutional pharmacies, and home health care companies . . . each dedicated to working with MSS in a team approach to enhance the quality of life and care of those they serve.

PHARMACOKINETICS

MEDICAL SUPPORT SYSTEMS, INC.
6660 Busch Boulevard
Columbus, Ohio 43229
(800) 822-4976

[PHARMACOKINETIC DRUG LIST]

CARDIAC	DIGOXIN (LANOXIN)
	DISOPYRAMIDE (NORPACE)
	PROCAINAMIDE (PRONESTYL)
	QUINIDINE
ANTICONVULSANTS	CARBAMAZEPINE (TEGRETOL)
	ETHOSUXIMIDE (ZARONTIN)
	PHENOBARBITAL
	PHENYTOIN (DILANTIN)
	VALPROIC ACID (DEPAKENE)
RESPIRATORY	THEOPHYLLINE
ANTIMANIA	LITHIUM
ANTICOAGULANTS	HEPARIN
	PROTAMINE
	WARFARIN
ANTIBIOTICS	AMIKACIN
	GENTAMICIN
	KANAMYCIN
	NETILMICIN
	TOBRAMYCIN
	VANCOMYCIN

PHARMACOKINETICS

SAMPLE FACILITY
KINETIC DATA SUMMARY

Territory Number 1101

Facility ______

Physician ______

Name ______ SS# ______

Height ______ Weight ______ Sex ___ DOB ______

Serum Creatinine ______ mg/dl Date ______

Albumin ______ gm/dl Date ______

Smoker: YES ___ NO ___

DX: ______

Other Medications: ______

SZ Frequency: ______ Controlled/Non-Con

Allergies: ______

Drug ______ Dosage Form ______

Strength ______ Times Dose Given ______

Regimen ______ Date Started ______

Serum Level ______ Time of Draw ______ Date ______

Initials ______ Data Collection Date ______ Billable ______

FOR HOME OFFICE USE:

Initial Use ______ Apparent Clearance ______ Series ___

Recommendations: ______

PK001A88

MEDICAL SUPPORT SYSTEMS
6660 Busch Boulevard
Columbus, Ohio 43229
1-800-322-4976

Sample Report

DIGOXIN DOSING SERVICE

page 1

-PATIENT, EXAMPLE PATIENT # EXAMPLE ROOM # EXAMPLE DATE 08/16/88

WEIGHT: 41.8 KG (92.0 LBS) LBW: 41.8 KG (92.0 LBS) AGE: 89 YEARS
HEIGHT: 59.0 IN. (149.9 CM) BSA: 1.33 m2 FEMALE DR. EXAMPLE

SERUM CREATININE: 2.1 MG/DL CALCULATED CREATININE CLEARANCE: 12.0 MLS/MN
DATE MEASURED: 08/14/88 BASED ON A WEIGHT OF: 41.8 (KGS ABW)

CASE SUMMARY

MS. EXAMPLE IS AN 89yo FEMALE DIAGNOSED WITH CHF, ASHD, COPD, AND DM. INCLUDED IN HER MEDICATION REGIMEN IS DIGOXIN TABLETS 0.25mg DAILY AT 0900. SHE IS PRESCRIBED NO CONCOMITANT ANTIARRHYTHMIC MEDICATION.

ON 8-14-88 A SERUM DIGOXIN LEVEL OF 2.1 ng/ml WAS DRAWN AT 0630. ON THAT SAME DATE A SERUM CREATININE OF 2.1 mg/dl WAS OBTAINED.

COMMENT AND SUGGESTION

RECOMMENDATION:

DIGOXIN TABLETS 0.125mg ALTERNATING WITH 0.25mg QOD

OR

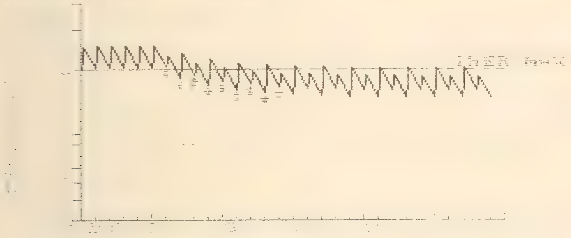
DIGOXIN TABLETS 0.125mg DAILY

MS. EXAMPLE LIES ABOVE THE NORMAL THERAPEUTIC RANGE WHILE ON HER PRESENT DIGOXIN REGIMEN. EITHER OF THE TWO RECOMMENDATIONS WILL PLACE HER WITHIN THAT RANGE.

DIGOXIN DOSING SERVICE

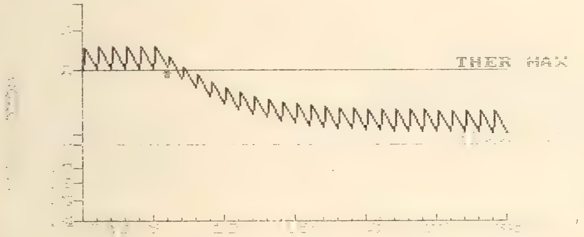
-PATIENT, EXAMPLE PATIENT # EXAMPLE ROOM # EXAMPLE DATE 08/16/88

DOSE REGIMEN 1



```
- 2  beginning concentration.
  0.250 mg Q 24H x 6.     ORAL TABLET  ABSORPTION TIME=2.00
  BIOAVAILABILITY=0.70  KE=0.010 /HR  T 1/2=66.6 HRS
  VD=305.1 LITERS (7.30 L/KG)  CL=3.2 L/HR
  0.125 mg Q 24H x 1.
  0.250 mg Q 24H x 1.
  0.125 mg Q 24H x 1.
  0.250 mg Q 24H x 1.
  0.125 mg Q 24H x 1.
  0.250 mg Q 24H x 1.
  0.125 mg Q 24H x 1.
  0.250 mg Q 24H x 1.
  0.125 mg Q 24H x 8.
```

DOSE REGIMEN 2



```
- 2  beginning concentration.
  0.250 mg Q 24H x 6.     ORAL TABLET  ABSORPTION TIME=2.00
  BIOAVAILABILITY=0.70  KE=0.010 /HR  T 1/2=66.6 HRS
  VD=305.1 LITERS (7.30 L/KG)  CL=3.2 L/HR
  0.125 mg Q 24H x 26.
```

Signature____________________________________ Date ______________________

Pharmacokinetic Drug Monitoring Service
Karen A. Weaver, R.Ph./Alice E. Rozic
William Chinn, MD

MEDICAL SUPPORT SYSTEMS
6660 Busch Boulevard
Columbus, Ohio 43229
1-800-322-4776

Sample Report

THEOPHYLLINE INITIAL GUIDELINES

page 1

-EXAMPLE, PATIENT   PATIENT # 999999999 1111   ROOM # SMILEY PLACE DATE 09/13/88

WEIGHT: 19.5 KG (43.0 LBS)   LBW: 19.5 KG (42.9 LBS) AGE: 5 YEARS
HEIGHT: 45.0 IN. (114.3 CM)   BSA: 0.79 m2   FEMALE   DR. WALKER

CASE SUMMARY

MS. EXAMPLE IS A 5yo FEMALE DIAGNOSED WITH ASTHMA. INCLUDED IN HER MEDICATION REGIMEN IS THEOPHYLLINE SUSTAINED RELEASE CAPSULES (SLO-BID) 150mg q12 HOURS AT 0800 AND 2000. SHE IS ALSO PRESCRIBED ALBUTEROL (PROVENTIL) INHALANT SOLUTION IN EFFORTS TO CONTROL SYMPTOMS ASSOCIATED WITH ASTHMA.

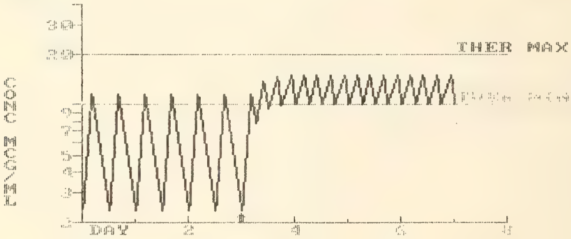
COMMENT AND SUGGESTION

RECOMMENDATION:
THEOPHYLLINE SUSTAINED RELEASE CAPSULES 150mg q6 HOURS

MS. EXAMPLE LIES BELOW THE NORMAL THERAPEUTIC RANGE WHILE ON HER PRESENT THEOPHYLLINE REGIMEN. THE ABOVE RECOMMENDATION SHOULD PLACE HER WITHIN THE RANGE THROUGHOUT THE DOSING INTERVAL.

**THIS CONSULTATION IS BASED ON POPULATION KINETICS BEST FITTING THE PATIENT AND DOES NOT ACCOUNT FOR PATIENT SPECIFIC VARIABLES.

DOSE REGIMEN 1



– 2.4 beginning concentration.
150.0 mg Q 12H x 6. THEOPHYLLINE SUSTAINED RELEASE ABSORPTION TIME=4.00
BIOAVAILABILITY=1.00 KE=0.200 /HR T 1/2=3.5 HRS VD=9.8 LITERS (0.50 L/KG)
CL=2.0 L/HR
150.0 mg Q 6H x 16.

Signature______________________________________ Date ______________________________

Pharmacokinetic Drug Monitoring Service
Karen A. Weaver, R.Ph./Alice E. Rozic
William Chinn, MD

MEDICAL SUPPORT SYSTEMS
6660 Busch Boulevard
Columbus, Ohio 43229
800-822-4976

Sample Report

CARBAMAZEPINE DOSING SERVICE

page 1

-EXAMPLE, PATIENT PATIENT # 999999999 9999 ROOM # SUNSET MANOR DATE 03/30/89

WEIGHT: 48.2 KG (106.0 LBS) LBW: 48.2 KG (106.0 LBS) AGE: 85 YEARS
HEIGHT: 59.5 IN. (151.1 CM) BSA: 1.42 m2 FEMALE DR. SMITH

CASE SUMMARY

MS. EXAMPLE IS AN 85yo FEMALE DIAGNOSED WITH SEIZURE DISORDER. INCLUDED IN HER MEDICATION REGIMEN IS CARBAMAZEPINE TABLETS 200mg QID AT 0900, 1300, 1700, AND 2100. THIS RESIDENT IS ALSO PRESCRIBED PHENYTOIN CAPSULES 100mg BID EFFORTS TO CONTROL HER SEIZURE DISORDER.

ON 3-10-89 A SERUM CARBAMAZEPINE LEVEL OF 4.5 mcg/ml WAS DRAWN AT 0600.

DATA SUMMARY

PATIENT IS ON 200.0 MGS ORAL TABLET EVERY 6.0 HOURS.
(BIOAVAILABILITY = 1.0, ABSORPTION TIME = 2.0 HOURS)
THE NEXT DOSE WAS TO BE GIVEN AT 0900 ON ANALYSIS DAY 1. A STEADY STATE LEVEL OF 4.5 MCG/ML WAS DRAWN AT 0600 ON ANALYSIS DAY 1.

PHARMACOKINETIC SUMMARY

THE APPARENT CARBAMAZEPINE CLEARANCE IS 8.27 L/HOUR.

BASED ON A VOLUME OF DISTRIBUTION OF 1.20 L/KG ABW THE ESTIMATED HALF-LIFE IS 4.8 HOURS AND EXPECT STEADY STATE IN 24.2 HOURS.
THE ESTIMATED VOLUME OF DISTRIBUTION IS 57.8 LITERS.

DOSAGE RECOMMENDATION

DOSE AND BLOOD LEVEL PROJECTIONS REFLECT ANTICIPATED ENZYME INDUCTION.
WHEN INITIATING THERAPY WITH CARBAMAZEPINE GIVE:
  25% OF THE DOSE THE FIRST WEEK,
  50% OF THE DOSE THE SECOND WEEK,
  75% OF THE DOSE THE THIRD WEEK,
  AND THE ENTIRE DOSE THEREAFTER.

ORAL TABLET (ABSORPTION TIME = 2.0, BIOAVAIL. = 1.00)
200.0 MGS EVERY 6 HOURS IS EXPECTED TO PRODUCE STEADY STATE LEVELS OF:
CP-MAX = 5.2 MCG/ML CP-AVE = 4.1 MCG/ML
CP-MIN = 2.9 MCG/ML THIS DOSE REPRESENTS 4.2 MGS/KG ABW.

ORAL TABLET (ABSORPTION TIME = 2.0, BIOAVAIL. = 1.00)
300.0 MGS EVERY 6 HOURS IS EXPECTED TO PRODUCE STEADY STATE LEVELS OF:
CP-MAX = 7.8 MCG/ML CP-AVE = 6.1 MCG/ML
CP-MIN = 4.4 MCG/ML THIS DOSE REPRESENTS 6.2 MGS/KG ABW.

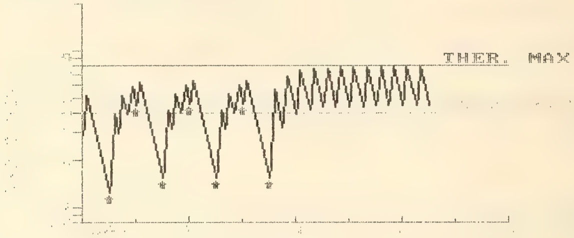
99-261 0 - 89 - 17

CARBAMAZEPINE DOSING SERVICE

page 2

-EXAMPLE, PATIENT   PATIENT # 999999999 9999   ROOM # SUNSET MANOR DATE 03/30/89

DOSE REGIMEN 1



– 2.9 beginning concentration.
200.0 mg Q 12H x 1.   ORAL TABLET ABSORPTION TIME=2.00
BIOAVAILABILITY=1.00 KE=0.143 /HR T 1/2=4.8 HRS VD=57.8 LITERS (1.20 L/KG)
CL=8.3 L/HR
200.0 mg Q 4H x 3.
200.0 mg Q 12H x 1.
200.0 mg Q 4H x 3.
200.0 mg Q 12H x 1.
200.0 mg Q 4H x 3.
200.0 mg Q 12H x 1.
300.0 mg Q 6H x 12.

COMMENT AND SUGGESTION

RECOMMENDATION:
CARBAMAZEPINE TABLETS 300mg q6 HOURS

MS. EXAMPLE LIES BELOW THE NORMAL THERAPEUTIC RANGE (WITH CONCOMITANT ANTICONVULSANT THERAPY THERAPEUTIC RANGE NARROWS TO 4-8 mcg/ml) WHILE ON HER PRESENT CARBAMAZEPINE REGIMEN. THE ABOVE RECOMMENDATION WILL PLACE HER WITHIN THAT RANGE THROUGHOUT THE ENTIRE DOSING INTERVAL.

THIS PATIENT WILL BENEFIT FROM A SERUM CREATININE DRAW.

Signature______________________________________ Date _________________________
Pharmacokinetic Drug Monitoring Service
Karen A. Weaver, R.Ph./William Chinn, M.D.

This clinical consult utilizes software developed and copyrighted by Data Med Clinical Support Services, Inc.

MEDICAL SUPPORT SYSTEMS
6660 Busch Boulevard
Columbus, Ohio 43229
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Sample Report

GENTAMICIN INITIAL GUIDELINES

page 1

-EXAMPLE, PATIENT PATIENT # 999999999 9999 ROOM # MERCY HOSPITAL DATE 09/19/88

WEIGHT: 96.4 KG (212.0 LBS) LBW: 86.8 KG (191.0 LBS) AGE: 29 YEARS
HEIGHT: 76.0 IN. (193.0 CM) BSA: 2.27 m2 MALE DR. SMITH

SERUM CREATININE: 1.4 MG/DL CALCULATED CREATININE CLEARANCE: 95.6 MLS/MN
DATE MEASURED: 09/19/88 BASED ON A WEIGHT OF: 86.8 (KGS LBW)

CASE SUMMARY

MR. EXAMPLE IS A 29yo MALE DIAGNOSED WITH PSEUDOMONAS AERUGINOSA PNEUMONIA. TODAY UPON ADMISSION A SERUM CREATININE VALUE OF 1.4 mg/dl WAS REPORTED.

A REQUEST FOR GENTAMICIN LOAD AND MAINTENANCE DOSING HAS BEEN RECEIVED BY THE PHARMACY STAFF.

PHARMACOKINETIC SUMMARY

ESTIMATES ARE BASED UPON LEAN BODY WEIGHT AND EXCESS BODY WEIGHT.

THE ESTIMATED HALF-LIFE = 2.4 HOURS.
THE ESTIMATED KE = 0.287 /HOUR.
THE ESTIMATED VD = 22.2 LITERS (0.23 L/KG ABW)
THE ESTIMATED CLEARANCE = 6.37 LITERS/HOUR.
EXPECT STEADY STATE IN 12.1 HOURS (0.5 DAYS).

The above estimations are based upon population values. The patient's actual pharmacokinetic parameters should be obtained as soon as feasible to insure optimum individualization of this patient's drug therapy.

LOADING DOSE

Raising the patient's GENTAMICIN concentration from 0.0 to 8.0 MCG/ML (an overall change of 8.0 MCG/ML) should require a loading dose of 205.0 MGS INTERMITTENT IV (2.1 mg/kg ABW) infused over 1.00 hour.

DOSAGE RECOMMENDATION

INTERMITTENT IV (INFUSION TIME = 1.0, BIOAVAIL. = 1.00)
190.0 MGS EVERY 8 HOURS IS EXPECTED TO PRODUCE STEADY STATE LEVELS OF:
CP-MAX = 8.3 MCG/ML
CP-MIN = 1.1 MCG/ML THIS DOSE REPRESENTS 2.0 MGS/KG ABW.

```
GENTAMICIN  INITIAL  GUIDELINES                              page 2
 -EXAMPLE, PATIENT   PATIENT # 999999999  9999    ROOM # MERCY HOSPITAL  DATE
09/19/88

DOSE  REGIMEN  1
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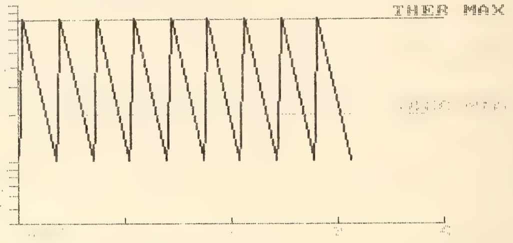

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— 1.1  beginning concentration.
  190.0 mg Q 8.3H x 9.    INTERMITTENT IV  INFUSION TIME=1.00
  BIOAVAILABILITY=1.00  KE=0.287 /HR  T 1/2=2.4 HRS  VD=22.2 LITERS (0.23 L/KG)
  CL=6.4 L/HR

COMMENT  AND  SUGGESTION

RECOMMENDATION:
                 GENTAMICIN LOAD:  205mg
                                   INFUSION TIME:  1 HR.
                                   PEAK TARGET CONCENTRATION:  8 mcg/ml


                MAINTENANCE DOSE:  190mg
                                   INFUSION TIME:  1 HR.
                                   DOSING INTERVAL:  8.25 HRS.
                                   PEAK CONCENTRATION:  8.3 mcg/ml
                                   TROUGH CONCENTRATION:  1.1 mcg/ml


BASED ON POPULATION PHARMACOKINETICS BEST FITTING THIS PATIENT, THE ABOVE
RECOMMENDATION WILL PLACE HIM WITHIN THE NORMAL THERAPEUTIC RANGE FOR
GENTAMICIN THERAPY.  TO OPTIMIZE INDIVIDUALIZATION OF PATIENT THERAPY,
SERUM GENTAMICIN LEVELS SHOULD BE OBTAINED AS SOON AS IS FEASIBLE.

Signature_______________________________________ Date __________________________
         Pharmacokinetic Drug Monitoring Service
         Karen A. Weaver, RPh/Alice E. Rozic
         William Chinn, MD
```
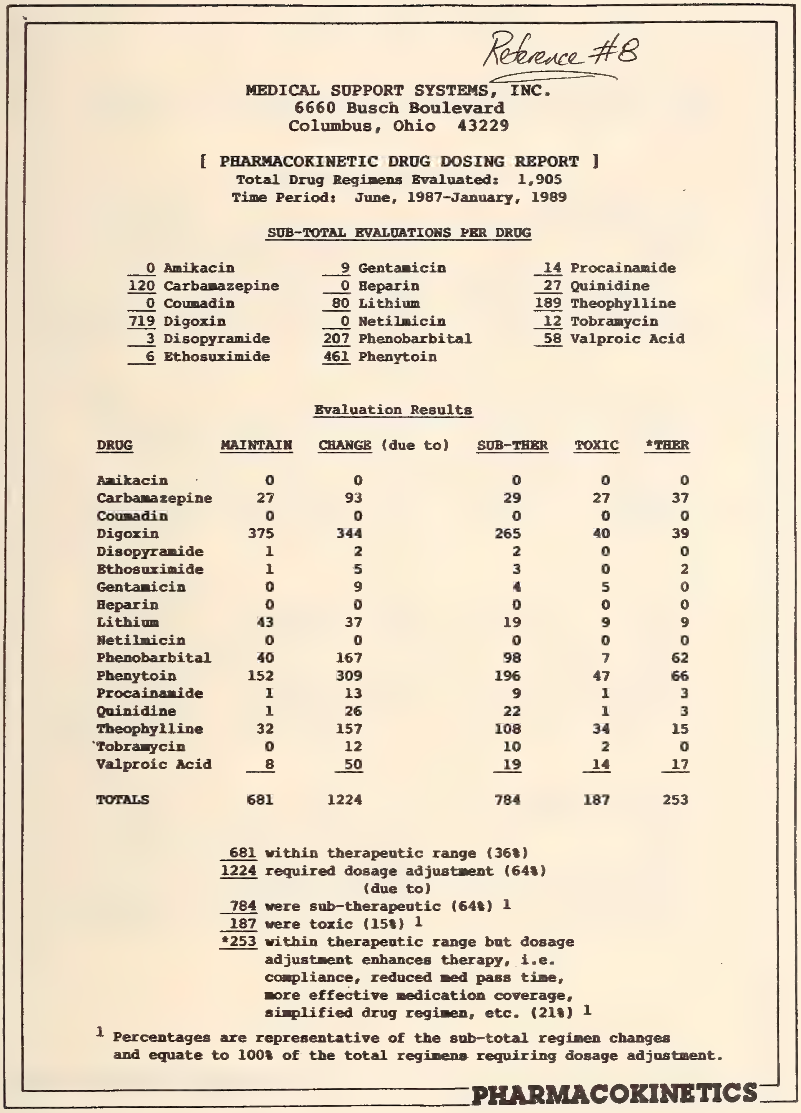



Reference #8

MEDICAL SUPPORT SYSTEMS, INC.
6660 Busch Boulevard
Columbus, Ohio 43229

[PHARMACOKINETIC DRUG DOSING REPORT]

Total Drug Regimens Evaluated: 1,905
Time Period: June, 1987-January, 1989

SUB-TOTAL EVALUATIONS PER DRUG

0	Amikacin	9	Gentamicin	14	Procainamide
120	Carbamazepine	0	Heparin	27	Quinidine
0	Coumadin	80	Lithium	189	Theophylline
719	Digoxin	0	Netilmicin	12	Tobramycin
3	Disopyramide	207	Phenobarbital	58	Valproic Acid
6	Ethosuximide	461	Phenytoin		

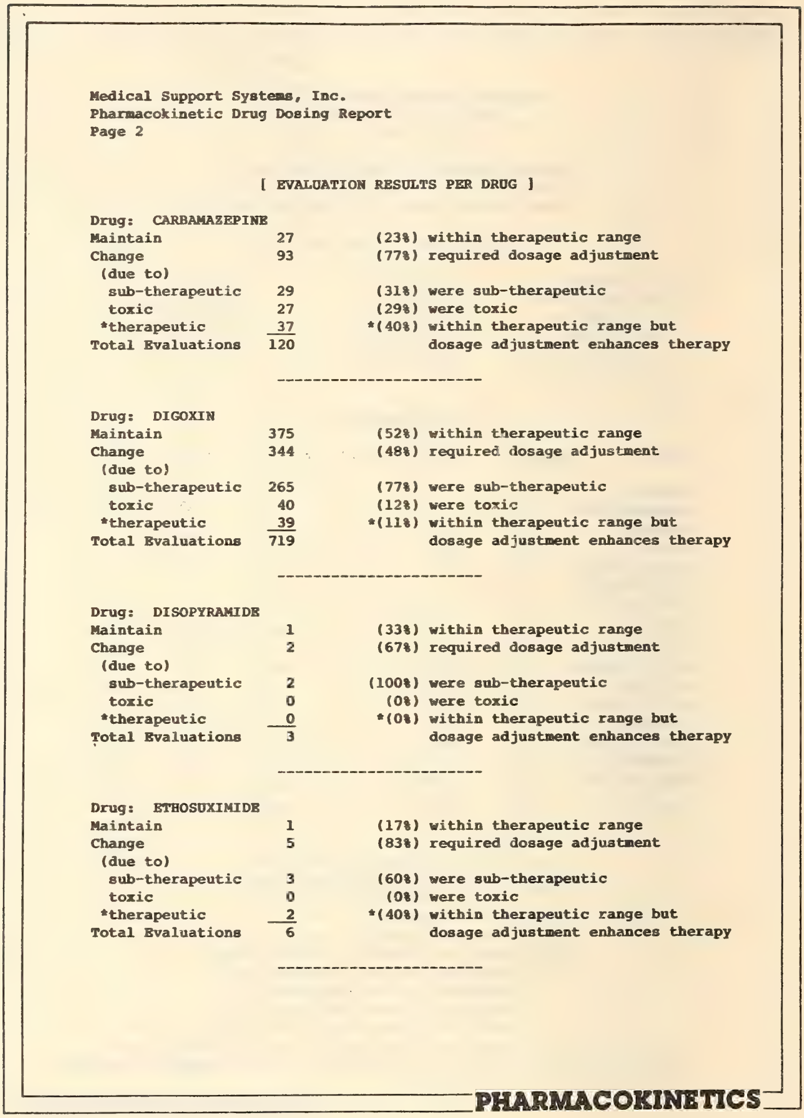
Evaluation Results

DRUG	MAINTAIN	CHANGE (due to)	SUB-THER	TOXIC	*THER
Amikacin	0	0	0	0	0
Carbamazepine	27	93	29	27	37
Coumadin	0	0	0	0	0
Digoxin	375	344	265	40	39
Disopyramide	1	2	2	0	0
Ethosuximide	1	5	3	0	2
Gentamicin	0	9	4	5	0
Heparin	0	0	0	0	0
Lithium	43	37	19	9	9
Netilmicin	0	0	0	0	0
Phenobarbital	40	167	98	7	62
Phenytoin	152	309	196	47	66
Procainamide	1	13	9	1	3
Quinidine	1	26	22	1	3
Theophylline	32	157	108	34	15
Tobramycin	0	12	10	2	0
Valproic Acid	8	50	19	14	17
TOTALS	681	1224	784	187	253

681 within therapeutic range (36%)
1224 required dosage adjustment (64%)
(due to)
784 were sub-therapeutic (64%) [1]
187 were toxic (15%) [1]
*253 within therapeutic range but dosage adjustment enhances therapy, i.e. compliance, reduced med pass time, more effective medication coverage, simplified drug regimen, etc. (21%) [1]

[1] Percentages are representative of the sub-total regimen changes and equate to 100% of the total regimens requiring dosage adjustment.

PHARMACOKINETICS



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Medical Support Systems, Inc.
Pharmacokinetic Drug Dosing Report
Page 2

                    [ EVALUATION RESULTS PER DRUG ]

Drug:  CARBAMAZEPINE
Maintain              27          (23%) within therapeutic range
Change                93          (77%) required dosage adjustment
 (due to)
  sub-therapeutic     29          (31%) were sub-therapeutic
  toxic               27          (29%) were toxic
 *therapeutic         37         *(40%) within therapeutic range but
Total Evaluations    120                dosage adjustment enhances therapy

                     -----------------------

Drug:  DIGOXIN
Maintain             375          (52%) within therapeutic range
Change               344          (48%) required dosage adjustment
 (due to)
  sub-therapeutic    265          (77%) were sub-therapeutic
  toxic               40          (12%) were toxic
 *therapeutic         39         *(11%) within therapeutic range but
Total Evaluations    719                dosage adjustment enhances therapy

                     -----------------------

Drug:  DISOPYRAMIDE
Maintain               1          (33%) within therapeutic range
Change                 2          (67%) required dosage adjustment
 (due to)
  sub-therapeutic      2         (100%) were sub-therapeutic
  toxic                0           (0%) were toxic
 *therapeutic          0          *(0%) within therapeutic range but
Total Evaluations      3                dosage adjustment enhances therapy

                     -----------------------

Drug:  ETHOSUXIMIDE
Maintain               1          (17%) within therapeutic range
Change                 5          (83%) required dosage adjustment
 (due to)
  sub-therapeutic      3          (60%) were sub-therapeutic
  toxic                0           (0%) were toxic
 *therapeutic          2         *(40%) within therapeutic range but
Total Evaluations      6                dosage adjustment enhances therapy

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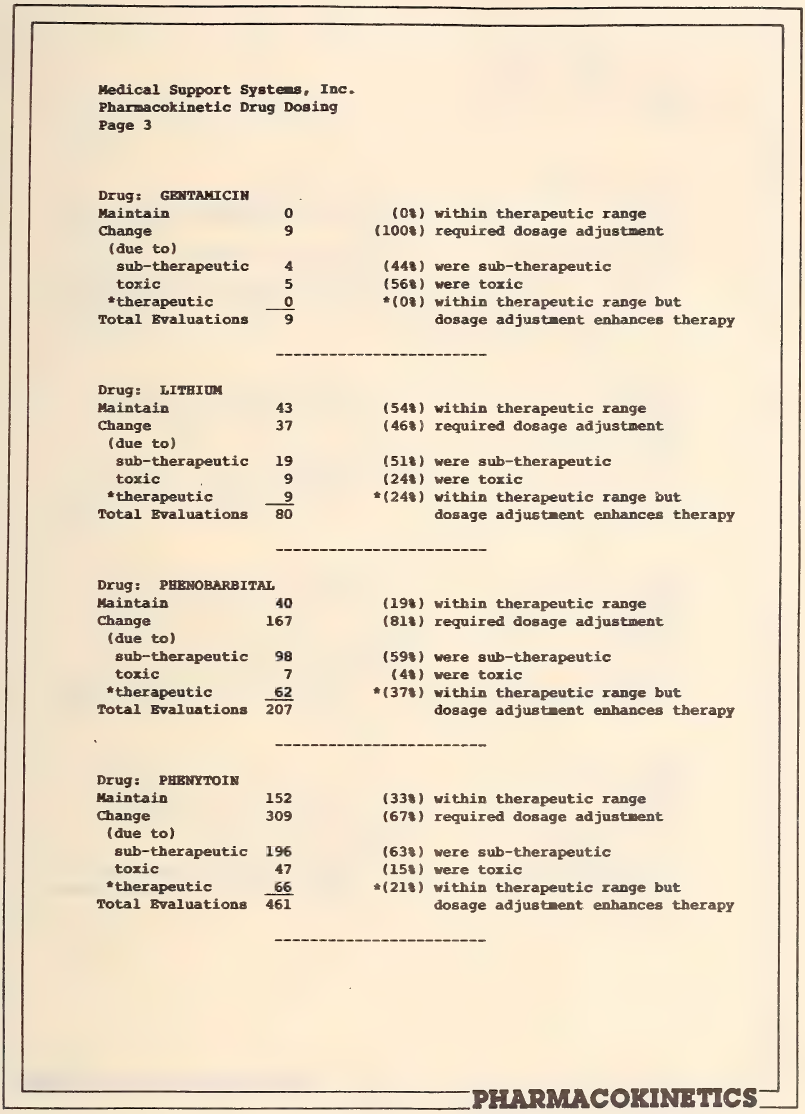
PHARMACOKINETICS



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Medical Support Systems, Inc.
Pharmacokinetic Drug Dosing
Page 3


Drug:  GENTAMICIN
Maintain              0          (0%) within therapeutic range
Change                9        (100%) required dosage adjustment
 (due to)
  sub-therapeutic     4         (44%) were sub-therapeutic
  toxic               5         (56%) were toxic
 *therapeutic       __0         *(0%) within therapeutic range but
Total Evaluations     9               dosage adjustment enhances therapy

                    ------------------------

Drug:  LITHIUM
Maintain             43         (54%) within therapeutic range
Change               37         (46%) required dosage adjustment
 (due to)
  sub-therapeutic    19         (51%) were sub-therapeutic
  toxic               9         (24%) were toxic
 *therapeutic       __9        *(24%) within therapeutic range but
Total Evaluations    80               dosage adjustment enhances therapy

                    ------------------------

Drug:  PHENOBARBITAL
Maintain             40         (19%) within therapeutic range
Change              167         (81%) required dosage adjustment
 (due to)
  sub-therapeutic    98         (59%) were sub-therapeutic
  toxic               7          (4%) were toxic
 *therapeutic       _62        *(37%) within therapeutic range but
Total Evaluations   207               dosage adjustment enhances therapy

                    ------------------------

Drug:  PHENYTOIN
Maintain            152         (33%) within therapeutic range
Change              309         (67%) required dosage adjustment
 (due to)
  sub-therapeutic   196         (63%) were sub-therapeutic
  toxic              47         (15%) were toxic
 *therapeutic       _66        *(21%) within therapeutic range but
Total Evaluations   461               dosage adjustment enhances therapy

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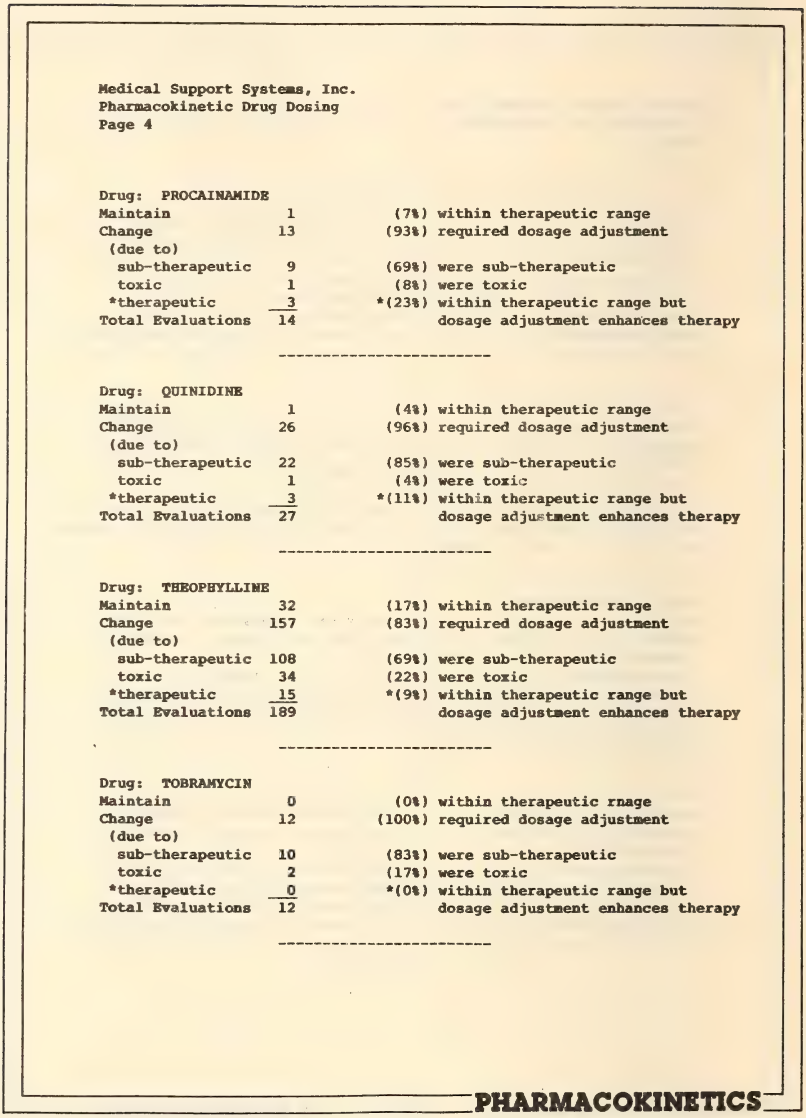
PHARMACOKINETICS



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Medical Support Systems, Inc.
Pharmacokinetic Drug Dosing
Page 4


Drug:  PROCAINAMIDE
Maintain              1          (7%) within therapeutic range
Change               13         (93%) required dosage adjustment
 (due to)
  sub-therapeutic     9         (69%) were sub-therapeutic
  toxic               1          (8%) were toxic
 *therapeutic         3        *(23%) within therapeutic range but
Total Evaluations    14               dosage adjustment enhances therapy

                     ------------------------

Drug:  QUINIDINE
Maintain              1          (4%) within therapeutic range
Change               26         (96%) required dosage adjustment
 (due to)
  sub-therapeutic    22         (85%) were sub-therapeutic
  toxic               1          (4%) were toxic
 *therapeutic         3        *(11%) within therapeutic range but
Total Evaluations    27               dosage adjustment enhances therapy

                     ------------------------

Drug:  THEOPHYLLINE
Maintain             32         (17%) within therapeutic range
Change              157         (83%) required dosage adjustment
 (due to)
  sub-therapeutic   108         (69%) were sub-therapeutic
  toxic              34         (22%) were toxic
 *therapeutic        15         *(9%) within therapeutic range but
Total Evaluations   189               dosage adjustment enhances therapy

                     ------------------------

Drug:  TOBRAMYCIN
Maintain              0          (0%) within therapeutic rnage
Change               12        (100%) required dosage adjustment
 (due to)
  sub-therapeutic    10         (83%) were sub-therapeutic
  toxic               2         (17%) were toxic
 *therapeutic         0         *(0%) within therapeutic range but
Total Evaluations    12               dosage adjustment enhances therapy

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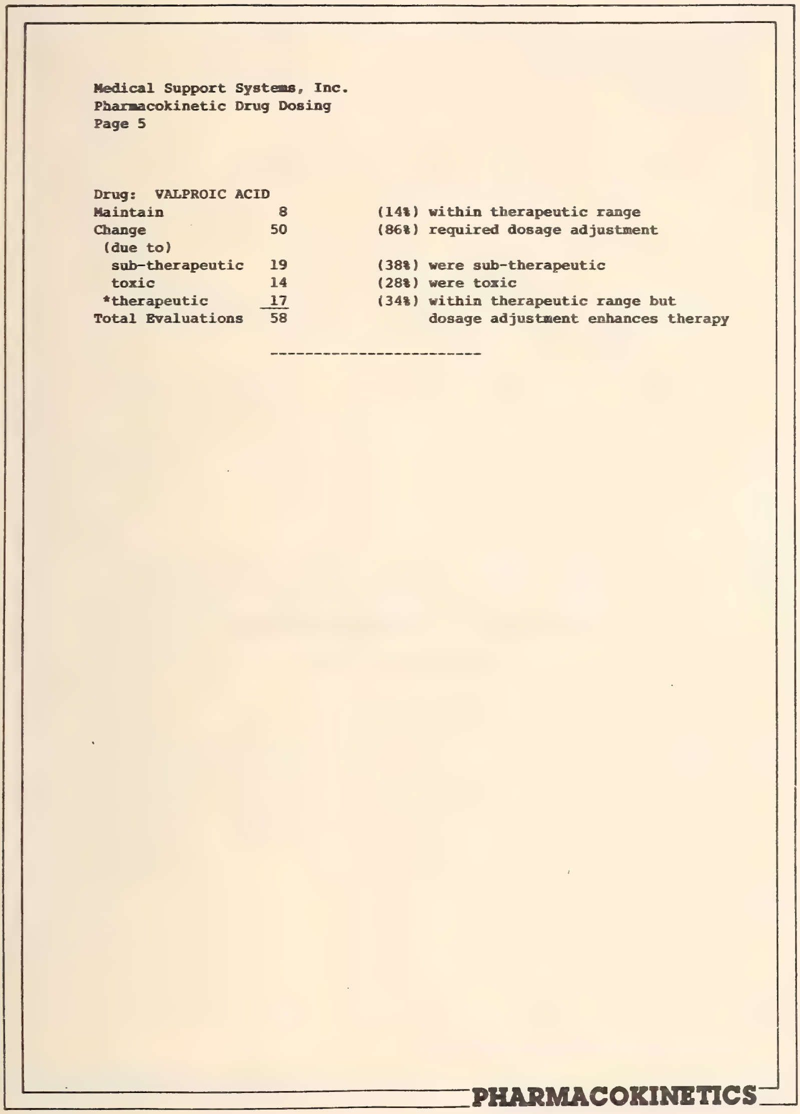
PHARMACOKINETICS



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Medical Support Systems, Inc.
Pharmacokinetic Drug Dosing
Page 5


Drug:  VALPROIC ACID
Maintain             8          (14%) within therapeutic range
Change              50          (86%) required dosage adjustment
 (due to)
  sub-therapeutic   19          (38%) were sub-therapeutic
  toxic             14          (28%) were toxic
 *therapeutic       17          (34%) within therapeutic range but
Total Evaluations   58                dosage adjustment enhances therapy

                    ------------------------
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PHARMACOKINETICS

MEDICAL SUPPORT SYSTEMS, INC.
6660 Busch Boulevard
Columbus, Ohio 43229
800-822-4976

Reference # 9

Pharmacokinetic Retrospective Study

February 21, 1989

PHARMACOKINETICS

PHARMACOKINETIC RETROSPECTIVE STUDY

(Cont'd)

Laboratory Evaluation

Total Number of Peak / Trough Draws: 98

	PEAK		TROUGH	
Number of Draws:	47	(48%)	51	(52%)
Drawn at Correct Time:	7	(15%)	20	(39%)
Drawn at Incorrect Time:	38	(81%)	29	(57%)
Draw Time Unknown:	2	(2%)	2	(2%)

NOTE: Twenty (20) draws had a value of <1.0 mcg/mL; therefore, could not be useful in pharmacokinetic analysis. Of these twenty draws, ten (10) were drawn at the correct time and ten (10) were drawn at the incorrect time.

Financial Impact

Charges for lab analyses yielding no useful information:	$3,086.10	(83%)
Charges for lab analyses yielding useful information:	674.70	(17%)
TOTAL CHARGES:	$3,733.80	(100%)

PHARMACOKINETICS

PHARMACOKINETIC RETROSPECTIVE STUDY

Time Period: 09/27/88 through 10/31/88

Total Possible Evaluations: 25

Pharmacokinetic Evaluations Performed: 21

Peak / Trough Analysis: 6

Bayesian Population Analysis: 15

Pharmacokinetic Evaluations Not Performed: 4

due to unavailable height: 3

weight: 2

both: 1

Evaluation Results

MEDICATION	MAINTAIN	CHANGE (due to)	SUB-THER	TOXIC
gentamicin	0	9	4	5
tobramycin	0	12	10	2
TOTALS	0	21	14	7

Percentage Results

0% Within Therapeutic Range

100% Required Adjustment in Therapy

67% Sub-therapeutic

33% Toxic

PHARMACOKINETICS

NDC.

MARK L. BRAUNSTEIN
President and
Chief Operating Officer

April 17, 1989

Select Committee on Aging
Sub-Committee on Human Services
U. S. House of Representatives
Washington, DC

Re: "Drug Abuse Among the Elderly"

Gentlemen:

On behalf of National Data Corporation, I want to thank you for the opportunity to present National Data's views on "Drug Abuse among the Elderly."

As explained in the attached statement, National Data has years of experience in the industries and technologies associated with the proposed point-of-service system. We support the use of the system for eligibility determination, claims adjudication and prospective review. We believe these needs can be served with currently available technology while insuring adequate system response time and reliability. Patient confidentiality can be controlled through adequate system controls. We would urge the Congress to encourage a broad implementation of the service as it pertains to the protection of Medicare recipients against drug misuse.

Please let me know if you have any questions or if we can provide you with any additional information.

Sincerely,

Mark Braunstein

MARK L. BRAUNSTEIN

Attachment

NATIONAL DATA CORPORATION *National Data Plaza* *Atlanta, Georgia 30329-2010* *(404) 728-2505*

Statement of

Mark L. Braunstein, M.D.
President and Chief Operating Officer
National Data Corporation

Before the

Select Committee on Aging

Sub-Committee on Human Services

U. S. House of Representatives

Hearings on

"Drug Abuse Among the Elderly"

Wednesday, April 19, 1989

Mr. Chairman and Members of the Committee:

BACKGROUND

National Data Corporation (NDC) has been in the business of providing systems for the automation of the practice of pharmacy since late 1976. National Data systems are widely utilized by over 3,000 pharmacies providing service to ambulatory patients (including those within staff model health maintenance organizations (HMO's) and patients within long term care and acute in-patient facilities.

National Data systems utilize a computer installed on-site, proprietary software developed by NDC and a variety of data bases which support real-time prospective review of proposed drug dispensing for a number of potential clinical errors. The systems also support monitoring of patient compliance with the physician's dispensing directions, as well as the distribution of patient educational information.

Since 1978, National Data has provided versions of its products to the worldwide system of in-patient and ambulatory care facilities operated by the Department of Defense (DOD). Currently over 200 systems are installed within DOD operated facilities. In the Washington, D.C. area alone, the system is installed at the Bethesda Naval Hospital and its ambulatory clinics, the Walter Reed Army Hospital and its ambulatory clinics, the Andrews Air Force Base hospital and its ambulatory clinics, the Portsmouth Naval Hospital and its extensive network of ambulatory clinics, as well as in the pharmacy facility located within the U. S. Capitol which services, among others, the members of Congress.

National Data Corporation believes that it has had unusually extensive experience in the development and successful operation of pharmacy management systems specifically designed to maintain patient drug profiles over large institutional specific populations. Our experience includes the utilization of these profiles along with clinical data bases to review proposed new medications for safety in light of known patient allergies, potential therapeutic overlap or potential drug interaction. We feel that we are quite familiar with the technical demands which are placed on such systems to provide responsive service in the face of the high volumes of transactions associated with large scale facilities, such as those supported by the DOD and major HMOs.

The management of National Data's Health Care Division, includes over a dozen health care professionals, many of whom occupy key management positions within the company. We believe that these personnel provide National Data with a clear understanding of the real world demands facing the practice of pharmacy.

National Data also operates the nation's largest network of point-of-sale devices for the processing of credit card payments from merchants. Recent data published by the Nilson Report, a well recognized industry trade publication, would indicate that National Data's share of the credit card terminal population currently is about 22%. In our current fiscal year, we will process well over 400 million point-of-sale transactions from this terminal population.

Additionally, since early 1988 National Data has utilized its credit card network and processing facilities to provide real time eligibility determination and claims adjudication services for pharmacy. Among our early clients for this service is California Blue Cross, on whose behalf we currently operate a network of point of service terminals and links to pharmacy computer systems reaching virtually every pharmacy in the state of California. At the present time, National Data processes in excess of one million real time transactions per month on behalf of its various health care clients. The Massachusetts Medicaid Real-time Eligibility Verification system (REVS) utilizes the NDC network.

We believe this combination of experiences places National Data in a strong position to understand the demands which will be placed upon the proposed nationwide point of service network in support of the Catastrophic Medicare prescription benefit program.

THE CATASTROPHIC MEDICARE PROGRAM

National Data has a great interest in the discussions currently underway concerning the use of the proposed nationwide point of service network to maintain patient drug profiles and provide prospective utilization review services similar to those historically offered by us as part of our pharmacy management systems. In view of our background and strong interest in this area, we wish to provide our comments and observations and hope these will be of benefit to this sub-committee as it considers the problem of drug misuse among the elderly.

The case seems to be clear that drug misuse by the elderly is a significant problem. While we can claim no particular knowledge of this matter other than our own experience in the field, we would certainly state that our sense of the problem is entirely consistent with conclusions and observations contained within the recent reports of the Inspector General and the Senate Special Committee on Aging. More pertinent to our expertise is the matter of the technical feasibility of developing and supporting a nationwide profile based system for the prospective review of potential drug abuse among elderly patients through the point of service system.

National Data began the development of its point of service real time pharmacy claims processing system over three years ago based on the rapid maturing of technology originally developed for the bank card industry, and our belief in the capabilities of this technology to serve the health care industry for the management of quality and cost. From the beginning, we viewed such systems as offering the potential for no less than three basic services:

1) Real time patient eligibility verification.
2) Real time administration and adjudication of claims.
3) Real time prospective review of proposed drug therapy (clinical adjudication).

Over the past three years, National Data has successfully developed and deployed a system providing the first two capabilities. As described earlier, NDC is successfully utilizing the system to provide service to a variety of clients. In our view, the successful provision of the clinical adjudication service rests not only upon the availability of appropriate technical skills, but upon the availability of proper informational data bases designed specifically to support high volume, real time transaction processing. Since we believe such data bases are not available commercially, we began the development of our data base nearly three years ago. That development project is essentially complete and in our view a service including profile based prospective review of proposed therapy is feasible within the confines of currently available technology and based upon capabilities contained within our current service as enhanced by the NDC developed data base.

THE ISSUES

Given the technical feasibility of a real-time system containing all three services the remaining issues relate to performance and confidentiality of data.

Performance is significant in any point-of-service system where the patient/customer must be served reliably and in a timely manner. The bankcard industry has successfully coped with volumes of transactions well in excess of those forecast under the new Medicare program. In fact, NDC's annual volume of bankcard transactions approaches those of the program. "End-to-End" response times in the bankcard industry are typically 15 seconds. Similar delays appear acceptable in the pharmacy. Moreover, several vendors of pharmacy management systems (including NDC) have perfected the capability to perform the real-time processing in the "background" allowing the pharmacist to perform other work on his computer while the processing is being performed.

While the complexity of the processing associated with pharmacy transactions clearly exceeds the bankcard situation, this can be remedied, with comparable performance, by the application of hardware resources matched to the resource requirements of the project. While this implies higher hardware costs, the hardware costs of transaction processing are usually a small part of the overall costs of the system. System reliability can be controlled through well-understood concepts of computer and network redundancy.

Confidentiality of data is to some extent a problem of program definition and structure. Financial systems employ controls (such as PIN numbers) to secure what are in essence electronic funds transfer systems at the point-of-sale. In our view the issue is reduced to one of adequate focus on the issue translating into adequate safeguards throughout the system. The potential benefits in patient care should not be sacrificed to an emotional concern about data confidentiality.

SUMMARY

National Data has years of experience in the industries and technologies associated with the proposed point-of-service system. We support the use of the system for eligibility determination, claims adjudication and prospective review. We believe these needs can be served with currently available technology while insuring adequate system response time and reliability. Patient confidentiality can be controlled through adequate system controls. We would urge the Congress to encourage a broad implementation of the service as it pertains to the protection of Medicare recipients against drug misuse.

AMERICAN MEDICAL ASSOCIATION
1101 VERMONT AVENUE, N. W. • WASHINGTON, D. C. 20005 • PHONE (202) 789-7400

AMA WASHINGTON
JOHN S. ZAPP, D.D.S.
Director, Division of Government Affairs

DEPARTMENT OF CONGRESSIONAL AFFAIRS
W. SCOTT WILBER
Director

STEPHEN C. DUFFY
Assistant Director

May 16, 1989

RECEIVED
MAY 16 1989
Cong. Thomas J. Downey

The Honorable Thomas Downey, Chairman
Subcommittee on Human Services
Select Committee on Aging
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

In connection with the hearing your subcommittee held on April 19, 1989 entitled "Drug Misuse Among the Elderly and Its Impact on Community Board Care," I have enclosed for your information a copy of a letter from the American Medical Association (AMA) to the Acting Administrator of the Health Care Financing Administration (HCFA) dated April 28, 1989. In this letter to Mr. Louis B. Hays, James H. Sammons, MD, the AMA's Senior Executive Vice President, expresses several concerns of the Association with regard to a HCFA Final Rule with Comment Period on the topic of Medicare and Medicaid; Requirements for Long Term Care Facilities. The Final Rule as proposed by HCFA fails to address the AMA's concerns which were expressed in the comments on an earlier Proposed Rule on this subject.

Of particular interest to your subcommittee vis-a-vis its April 1989 hearing are our comments on the issue of whether patients in Long Term Care Facilities should be allowed to self-administer drugs without the express approval of a physician. The Association strongly objects to HCFA's proposed policy and I thought it appropriate to bring our position to your attention.

If I can be of further assistance or provide you with any additional information on this or other health-related topics, please do not hesitate to contact me.

Sincerely,

Stephen C. Duffy

SCD/ptb
Enclosure

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO, ILLINOIS 60610 • PHONE (312) 645-5000 • Fax (312) 645-4184 • Telex 28-0248

JAMES H. SAMMONS, M.D.
Executive Vice President
(645-4300)

April 28, 1989

Louis B. Hays
Acting Administrator
Health Care Financing Administration
Department of Health and Human Services
Attention: BERC-390-FC
P.O. Box 26676
Baltimore, Maryland 21207

RE: Final Rule with Comment Period: "Medicare and Medicaid; Requirements for Long Term Care Facilities." Federal Register of February 2, 1989 (54 F.R. 5316).

Dear Administrator Hays:

The American Medical Association is pleased that many of our earlier comments and suggestions regarding the Health Care Financing Administration's (HCFA) original proposal for Medicare and Medicaid Conditions of Participation for Long-Term Care Facilities (52 F.R. 38582) were addressed in the Final Rule, "Medicare and Medicaid; Requirements for Long Term Care Facilities," published with a comment period in the February 2, 1989, Federal Register (54 F.R. 5316). We are particularly pleased that you have sought further public comment on this important series of regulations. Hopefully, this process of seeking further public input on major regulatory initiatives following substantive changes that are in response to public comments will establish a precedent for future regulatory procedures.

The AMA is troubled that two major concerns expressed by this Association in its original comments to the Proposed Rule were not addressed in the Final Rule. First, the term "patient" has been eliminated from the Requirements, leaving the impression that the underlying medical reasons for which many individuals are placed in long-term care facilities may be overlooked, to the detriment of those patients. Second, we must repeat our strong objection to the policy of allowing patients in long-term care facilities to self-administer drugs without the express approval of a physician, leaving the safety of long-term care facility patients in jeopardy. Further, we ask that the physician's role in signing assessments and overseeing medical care be clarified to ensure that the Requirements and best interests of patients will be addressed.

Patient/Resident

In our initial comments to the Proposed Rule, the AMA strongly opposed HCFA's intent to replace the long-used term "patient" with "resident" in the Conditions of Participation. We continue to believe that use of the term "resident" in the Requirements is inappropriate because the term bears little relationship to the reason individuals receive long-term care under the Requirements. Under both the Medicare and Medicaid programs, an underlying medical condition must exist before institutional coverage is allowed. Under these Requirements, care must be provided in either a skilled nursing facility or an intermediate care facility, where medical care must be made available. Also, the Requirements mandate that an individual cannot be admitted to a facility without a physician's orders for the resident's immediate care.

The AMA is deeply concerned that the elimination of the term "patient" implies a change of focus in long-term care that will result in the medical needs of individuals in long-term care facilities becoming secondary to custodial needs. This change would occur, ironically, at a time when long-term care facilities are experiencing dramatic rises in level of medical care needs that they must address. With the limitations that have been placed on hospital care reimbursement in recent years, patients are being discharged to long-term care facilities with substantial medical needs. It is difficult to understand how or why that person's status should suddenly become "resident." To avoid confusion, use of the term "resident" should be limited to describing individuals who reside in facilities providing services that are primarily custodial, such as retirement communities, congregate facilities, or boarding homes.

While the AMA strongly urges that the term "patient" be used in the final Requirements to reflect the reason individuals are placed in long-term care, we understand the concern of many that "patient" may not always represent the reason some individuals remain in long-term care facilities. The Joint Commission on Accreditation of Healthcare Organizations has recognized the dual purpose of long-term care. In the Joint Commission's Long Term Care Standards, the term "patient/resident" is used for an individual in long-term care (Long Term Care Standards Manual, Joint Commission on Accreditation of Healthcare Organizations, 1988). If HCFA is committed to using the term "resident" in the final Requirements, the AMA strongly urges that HCFA follow the Joint Commission's lead and use the "patient/resident" terminology.

Self-Administration of Drugs

The AMA's original comments to the proposed Conditions of Participation included strong opposition to the policy of allowing patients in long-term care facilities to self-administer drugs without a physician's authorization. The Association remains adamant that this policy endangers the health and well being of long-term care patients and unnecessarily complicates the administration of long-term care facilities. That the policy has been elevated to the level of a patient "right" is particularly troublesome.

Unfortunately, in HCFA's comments to the proposed Conditions and the new Requirements, this issue has been too narrowly defined as one of patient autonomy. While the appropriate level of autonomy of long-term care patients should always be encouraged and even facilitated, as should the autonomy of patients in any health care setting, other practical issues have not been given due consideration in the face of HCFA's commitment to what is, in substance, a highly symbolic provision.

Overlooked is the fact that this new policy creates a blanket trial and error system for determining who is capable of self-administering medications. As stated in the preamble to the Requirements, "(i)f a drug self-administering resident makes an error in drug administration, the facility should reassess that resident's capability." For some individuals, that reassessment might very well come too late.

This policy also leaves long-term care facilities with a confusing system of responsibilities for drug administration and at far greater risk of error and liability pitfalls. By eliminating the traditional assumption that a physician determines when a patient can self-administer medication, this policy merely shifts to the facility the responsibility for determining when a patient can not self-administer, a complicated medical determination that only a properly trained individual health care practitioner can make, in most instances a physician under state law.

It also should be understood that this policy places the right of the individual patient over the safety of the long-term care population as a whole. Although the creation of this right is well-meaning, it gives the facility an increased burden of protecting the safety of the patient population, some of whom may be incapable of protecting themselves in a setting where self-administration of drugs is the norm. It is inconceivable that a long-term care facility would want to take on these added responsibilities.

Autonomy and the self-determination of long-term care patients, where possible, should be the rule for all care and every activity occurring in a long-term facility. An individual's ability to self-administer medications is only one of a wide variety of ways that autonomy can be protected. The Requirements should not put at risk the population of long-term care facilities or make the administration of long-term care facilities unnecessarily burdensome in order to make this single point.

Physician's Role in Assessments

The AMA urges that language be added in the Requirements to clarify the role of the physician in conducting periodic assessments. In Section 483.20, "Level A requirement: Resident assessment," Subsection (c) states: "Each assessment must be conducted or coordinated, with the appropriate participation of health professionals." This language implies that the involvement of a physician would be required in certain circumstances, for example, after a significant change in the resident's physical or mental condition arises.

In the event of such a change, it should be required that the patient's attending physician be involved in the performance of the medical assessment and coordination of health care services, and the physician should be required to sign the assessment. For the protection of the patient, we urge that such language be added to ensure that this necessary step is taken.

Conclusion

Except for the concerns that we have outlined here, the AMA believes that important progress has been made in bringing about needed change in long-term care facilities through the Medicare and Medicaid programs. We urge that the concerns we have shared be addressed so that the Requirements for Long-Term Care Facilities will be able to have the positive impact on patient care and safety that HCFA intends.

Sincerely,

James H. Sammons, M.D.

JHS/dlh
4927p

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DESIGNS, INC.

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RECEIVED
MAY 9 1989
Cong. Thomas J. Downey

1 May 1989

Congressman Tom Downey
U.S. House of Representatives
2232 Rayburn House Office Building
Washington, DC 20515

Dear Congressman Downey:

Thank you for providing this opportunity for Health Information Designs, Inc. to submit written testimony for the April 1989 hearings on "Drug Misuse Among the Elderly and It's Impact On Community Based Care." Sean Hornbeck has been very helpful in facilitating our participation.

Health Information Designs, Inc. has been in the therapeutic drug utilization business since 1978. Our experience demonstrates that tDUR can improve quality of care and produce significant savings in Medicare costs due to inappropriate use of pharmaceuticals. We believe that the Medicare program and the nation's elderly can benefit from the inclusion of tDUR at the outset of the Medicare prescription drug program. Our recommendations for Medicare implementation of tDUR are included in the testimony.

If I can provide any additional information, please do not hesitate to call me.

Sincerely,

M Lee Morse

M. Lee Morse
President

STATEMENT OF
Health Information Designs, Inc.

Prepared for the

U.S. House of Representatives
Select Committee on Aging
SubCommittee on Human Services

"Drug Misuse Among the Elderly and Its Impact on Community Based Care"

May 1, 1989

On behalf of Health Information Designs, Inc., I am very pleased to have this opportunity to provide testimony for the House Select Committee on Aging Subcommittee on Human Services. We believe that the Congressional mandate for implementation of drug utilization review under the Medicare Catastrophic Coverage Act of 1988 is clear and indicates an appreciation of the availability of operational drug utilization review programs and technologies.

Over the last several months, various interested parties have expressed concerns about the feasibility of implementing a clinical, quality-of-care-oriented drug utilization review program as specified in the legislation. Since HID is currently providing therapeutic drug utilization review services to millions of Americans in both public and private health care programs, we believe it is important to bring to your attention at this time experience-based information on the capacity of such programs to address Medicare's legislative requirements.

Our experience indicates that available technology and expertise can in fact be assembled to assure implementation by January 1, 1991 of a therapeutic drug utilization review (tDUR) program which addresses the quality-of-care expectations of the Congress for the Medicare Catastrophic Drug Program. Our experience further suggests that such quality-of-care drug utilization review functions will yield savings in Medicare pharmaceutical, Part A and Part B expenditures more than sufficient to pay for implementation and operation of the therapeutic drug utilization review program.

* * * * *

Health Information Designs has been developing and operating therapeutic drug utilization review systems since 1978. Some of HID's initial DUR developmental efforts were funded in part under a 1977 HCFA grant which led to implementation of the Minnesota Medicaid DUR program referred to in the HHS Inspector General's report on Medicare Drug Utilization Review. Currently, HID manages therapeutic drug utilization review programs for a variety of health benefit programs encompassing over 7 million individual beneficiaries in 48 states. The focus of each of these therapeutic DUR programs is to identify and correct drug therapy conflicts with the potential to cause or exacerbate illness. HID is providing DUR services to 7 state Medicaid agencies and other publicly funded health care benefit programs. Included among these is the Pennsylvania PACE Drug Program covering 500,000 elderly, through which HID has gained specialized experience and insight into operating therapeutic drug utilization review in a geriatric population. HID is also managing therapeutic drug utilization review programs for numerous private health care groups including self-insured employers, insurance companies and Health Maintenance Organizations. Nearly all of these programs include retirees and overall about 40% of the population monitored by HID is age 60 and older.

Each month HID processes approximately 20 million claims transactions encompassing drug, disease and medical procedure encounters. These data are merged and used to update patient-specific, longitudinal history files of the 7 million lives HID currently monitors. HID employs over 15 consensus panels of physicians, clinical pharmacists and other health professionals who establish and update the therapeutic risk criteria used to identify potentially problematic drug therapies. Monthly HID generates approximately 20,000 risk alert "profiles" on patients exhibiting potentially inappropriate or suboptimal drug therapy. These profiles are forwarded to over 200 specially-trained clinical monitors located throughout the United States whose role is to review the generated profiles and determine whether they represent clinically relevant potential drug therapy problems. As a result of these expert clinical assessments, approximately 10,000 Alert letters are being issued each month to physicians in 48 States.

HID's therapeutic drug utilization review programs have yielded marked improvements in patient care and reductions in both hospitalizations and pharmaceutical reimbursements. Demonstrated savings in pharmaceuticals and remedial care services have generally been more than 10 times the client's annual investment in therapeutic drug utilization review.

HID also conducts epidemiologic research in the area of prescription drugs. Since 1978, HID has been responsible to the U.S. Food and Drug Administration (FDA) for developing and operating technologies using health care claims data to identify adverse effects of prescription drugs. HID is continuously designing and executing epidemiologic risk protocols to identify unexpected adverse outcomes of pharmaceutical use within its managed care pharmaceutical benefit program data bases.

Results of HID's research efforts in the field of pharmaco-epidemiology have been published in refereed medical journals.[1]

* * * * *

Based on Health Information Designs, Inc.'s experience, we have several recommendations for implementation of Medicare's drug utilization review program:

I. *The Congressional mandate for DUR should be viewed as specifically incorporating quality-of-care oriented therapeutic drug utilization review (tDUR).*

II. *Therapeutic drug utilization review should be regarded as a distinct UR function and should be operationally separated from the program integrity/fraud and abuse/audit functions of the fiscal intermediaries/processors.*

III. *A phased approach would assure timely and effective implementation of a therapeutic drug utilization review program.*

> Effective implementation of therapeutic drug utilization review will yield substantial savings in Medicare's medical care costs (e.g., hospitalizations, physician visits, etc.). We believe that failure to implement an effective tDUR program at the outset of the Medicare prescription drug program will exacerbate the elderly's drug use problems as access barriers are reduced.

I. *The Congressional mandate for DUR should be viewed as specifically incorporating quality-of-care oriented therapeutic drug utilization review (tDUR).*

In enacting the Medicare Catastrophic Coverage Act of 1988, Congress was clearly concerned about the quality-of-care implications of the new prescription drug benefit coverage. For this reason, it specifically mandated in Section 202(b) of the Act that the Secretary establish a program to address drug utilization from a quality-of-care perspective, including identification of and education of physicians and pharmacists concerning:

- "Instances and patterns of unnecessary or inappropriate prescribing or dispensing practices;
- Instances or patterns of substandard care; and
- Potential adverse drug reactions."

Substantial evidence was presented to the Congress establishing the link between inappropriate use of prescription drugs and adverse therapeutic outcomes, including significant numbers of hospitalizations due to drug-induced illness, adverse drug reactions, and drug therapy conflicts. The HHS Inspector General's report documents these problems. These findings are consistent with our own experience and other research from around the world. Therapeutic drug utilization review is focused on these quality-of-care problems. It addresses high risk drug therapies which have potential to cause or worsen illness, necessitating hospitalization and other remedial care to treat these drug-induced disorders.

Under therapeutic DUR programs, clinical communications with physicians involved in high risk drug therapies are causing changes in how these physicians prescribe for their patients. In HID's programs, 70% of the physicians receiving "risk alert" letters respond by discontinuing drug treatment, changing drug amount or frequency of refill, or switching to a safer drug. Overall 30% of the alerts issued result in complete discontinuation of the drug which was the subject of the alert.

Therapeutic drug utilization review is the sole patient-specific, intervention-based DUR initiative for outpatient drug benefit programs having a demonstrable, timely impact upon quality of patient care.

II. *Therapeutic drug utilization should be regarded as a distinct UR function and should be operationally separated from the program integrity, fraud/abuse, and audit functions of the fiscal intermediaries.*

The Medicare Catastrophic Coverage Act of 1988 mandates utilization review functions in addition to those having a quality-of-care orientation, including UR functions relating to program integrity and fraud/abuse monitoring. While various activities may be included under the "drug utilization review" rubric, our experience suggests that it will be important to distinguish among three DUR functions:

- Quality assurance (therapeutically-oriented drug utilization review), targeted on identification of drug conflict situations, drug-induced illnesses and inappropriate use of drugs;

- Cost containment focused utilization review, involving, for example, use of generics, refill patterns, or ingredient costs;

- Fraud and abuse targeted utilization review involving unauthorized prescribing, dispensing or consumer usage of prescription drugs.

These three utilization review functions are not mutually exclusive but complementary. Effective therapeutic utilization review can have a demonstrable impact on costs, reducing utilization of drugs and lessening the use of medical services attributable to drug induced illnesses. However, we believe that for policy and management reasons, it is important to maintain a conceptual and operational separation between therapeutic DUR and program integrity or fraud and abuse focused tasks.

- The professional skills and expertise required for therapeutic DUR are different than those required to conduct administrative audits and fraud/abuse reviews. Therapeutic DUR requires experience in clinical pharmacy and epidemiology not required in claims processing or fraud/abuse monitoring.

- The therapeutic DUR management information system is more specialized, requiring patient-specific, longitudinal drug therapy data, preferably linked with diagnosis data. The DUR MIS requires expert clinical algorithms and experienced professionals for interpretation of data. Conventional claims processing information systems are designed primarily for claims adjudication and generally do not involve clinically-based interventions with providers.

- The public's and medical profession's growing concerns for assuring quality in a cost-containment driven era underscore the desirability of maintaining separate authorities for distinct fiduciary responsibilities. The therapeutic DUR program should not be perceived as another means for denying payment.

- In maintaining separate responsibilities, potential conflicts of interest and professional skepticism can be minimized and the integrity of the programs enhanced.

- Also, separation of functions could minimize potential liability problems arising from concerns that cost-containment objectives are driving therapeutic utilization review decisions.

Medicare has already distinguished between quality assurance review and fraud and abuse type audits, as evidenced by HCFA's PRO contracts covering Parts A and B:

- The PROs are responsible for monitoring utilization decisions related to quality and access to appropriate services.

- HCFA contracts directly with PROs that serve as independent entities charged with conducting clinically-oriented utilization review.

- The PROs are independent of the Medicare fiscal intermediaries and carriers that are primarily responsible for processing claims, providing required cost and utilization reports, and implementing payment review audits pertinent to cost containment.

The considerable management responsibilities associated with operating tDUR programs have the potential to overburden the fiscal intermediaries, who will already have a substantial management agenda in operationalizing the basic P.O.S. systems and program integrity UR requirements.

We recommend that a separate responsibilities model by requiring different entities to manage the distinguishable responsibilities for:

- Therapeutic drug utilization review/quality assurance; and
- Program integrity/fraud/abuse monitoring.

Given the implementation time constraints, we urge that HCFA contract with entities that have a demonstrated track record in designing, implementing and managing a therapeutic drug utilization review program. The January 1989 Inspector General's report on "Medicare Drug Utilization Review" found that most Medicaid DUR programs focus on program integrity rather than quality-of-care problems. The Minnesota Medicaid therapeutic DUR program was highlighted as offering one of the most sophisticated designs for addressing quality-of-care issues. The operational therapeutic DUR systems should serve as the basis for developing a Medicare tDUR program.

Performance related criteria for identification of potential therapeutically-oriented drug utilization review contractors should include the following demonstrated expertise and experience:

- Previous design and operation of outpatient pharmaceutical drug utilization review programs.
- Capacity to manage complex data systems including millions of patient-specific records and to link diagnosis data with prescription records in developing longitudinal, patient-specific profiles.
- Use of scientifically based DUR protocols for identifying potential drug therapy conflicts and adverse drug effects in a quality assurance mode.
- Operational epidemiologic-based systems for reviewing claims data, identifying potential problems and communicating with physicians and pharmacists in a clinical mode.
- Analytic skills in producing research quality reports in the health care field.
- Demonstrated experience in performing these functions for a cross-section of the population, including privately insureds, retirees, and Medicaid recipients, which would facilitate cross-system comparisons.

III. *A phased approach would assure timely and effective implementation of a therapeutic drug utilization review program.*

The Medicare Catastrophic Coverage Act mandates a role for pharmacists in counseling patients on "the appropriate use" of drugs and "potential interactions" between dispensed drugs. There is debate, however, as to the role that electronic point-of-sale (P.O.S.) technology, to be employed for eligibility verification and claims adjudication functions, should also be relied upon initially to support the pharmacist's quality-of-care UR functions.

HID recommends a phased approach to implementation of the quality-of-care, therapeutic drug utilization review functions contemplated under the Medicare Catastrophic Drug Program.

This "phasing in" of therapeutic drug utilization review functions effective January 1, 1991 might be accomplished as follows:

Phase I:

- Retrospective reviews and profiling based upon continuous monitoring of claims data, with written communications from DUR clinical monitors to physicians involved in potential drug therapy problems.
- Complementary education, counseling and technical assistance to physicians, pharmacists and patients based on findings of retrospective reviews. In dealing with the full-range of potential drug risk problems, it is important to include patient compliance education since failure to follow the prescribed drug regime can compromise health status.
- Follow-up evaluations to ascertain effects of DUR interventions on physician prescribing practices, beneficiary drug use, and longer-term beneficiary medical costs for specified conditions.

Phase II

- Continuation of retrospective review and interventions for those therapy problems which are not critically time dependent in nature.
- Establishment of centralized "real time" Pharmaceutical Conflict Intervention Centers (PCIC) linked electronically to the participating pharmacies in the region. The PCIC specialists would have access to the full patient profile, which could be reviewed without the need for an "open-line" or a "full profile" transmission to the pharmacy. These PCIC's would deal on a prospective basis with those alerts which involve an immediate health threat. The PCIC's would communicate back to pharmacies (either by

phone or terminal-based message) concerning those potential problems which can be addressed by the pharmacist (i.e., drug interactions, too frequent refills, allergic reactions). In other instances, where immediate attention of the prescribing physician to the apparent problem is required, the PCIC specialist could contact the physician by telephone to review the case and report back to the pharmacist appropriate dispensing instructions.

HID feels that this two-phase approach is in keeping with the legislative mandate and advisable for a number of reasons, including the following:

- Given the technical hurdles to be overcome, there is reason to be concerned about whether a P.O.S. system capable of supporting clinically-oriented drug utilization review functions can be fully functional by January 1, 1991. In light of this, sole reliance upon a P.O.S. UR approach could jeopardize HCFA's ability to be in compliance with the quality-of-care DUR mandate on the effective date. Initiating the Medicare Catastrophic Drug Program with a retrospective therapeutic drug utilization review program employing proven technology will assure compliance with the legislative mandate for a fully-operational quality-of-care DUR program on January 1, 1991.

- Initiating the Medicare Catastrophic Program with a retrospective therapeutic DUR program would permit the regional processors to focus their efforts initially on fully operationalizing and resolving problems in the basic P.O.S. drug claims submission and eligibility verification technology. Since this technology must be functioning efficiently to support any P.O.S. quality-of-care DUR application, HID feels it is advisable to assure refinement of the basic P.O.S. system before relying upon that system to support the program's quality-of-care DUR function.

- Implementation of a retrospective therapeutic DUR program on January 1, 1991 will assure access to quality-of-care DUR functions for those beneficiaries who receive drugs from pharmacies not yet operating a fully functional P.O.S. system on January 1, 1991. Given the uncertainty about the degree of penetration of P.O.S. technology which can be expected by January 1, 1991, this strategy again helps to assure compliance with the Congress' expectation that a quality-of-care DUR program will be in place program-wide on the implementation date.

- A phased approach to implementation of the therapeutic DUR program will provide an opportunity to define, based upon actual claims submission experience, the optimum P.O.S.-based therapeutic risk criteria and prospective alert procedures before introducing them nationwide into the P.O.S. DUR mode, where misinterpretation, incomplete data and system failures could actually be detrimental to quality-of-care. HID finds merit in the American Pharmaceutical Association's (APhA) recommendation that HCFA consider a "demonstration project" of on-line quality-of-care DUR capabilities prior to nationwide implementation of such a system.

- Requiring tDUR on the effective date will assure an opportunity to realize significant savings in Part A expenditures. In fact, without such a program in place, there is potential to see an increase in Part A expenditures because of elevated levels of drug-induced illness due to improved access to drugs among the elderly.

HID believes that a retrospective therapeutic DUR program under the Medicare Catastrophic DUR Program can be designed to effectively function as a "concurrent" tDUR program. The rapid access to claims data which will be possible via the P.O.S. systems will permit daily updating of Medicare beneficiary patient-specific drug experience profiles. Therapeutic risk criteria can be passed on a semi-weekly basis against the updated profiles. High risk profiles identified through computer analysis can be provided immediately to expert clinical reviewers. Those worthy of immediate action could be subject to a priority transmission process. Other less time-dependent drug therapy conflicts might trigger a written communication to the physician. HID anticipates that the retrospective therapeutic drug utilization review program implemented for the Medicare Catastrophic Drug Program should result in communications to physicians about potentially detrimental drug therapy practices within a few days following dispensing of the drug which is the subject of the alert.

* * * * *

Therapeutic drug utilization review offers a positive approach to cost containment.

HID's experience in performing therapeutic drug utilization review suggests that the Medicare program can expect to achieve significant savings in costs of remedial care required to treat drug-induced and exacerbated illness. These savings will substantially exceed the costs of implementing and operating the tDUR system.

Thus, while therapeutic drug utilization review programs are not targeted on reducing access to the benefit, available studies clearly indicate that substantial savings will be realized through a reduction in both prescription drug use and remedial medical care services. The magnitude of drug therapy conflicts and potential for savings can also be demonstrated by considering a composite of HID's clients "pre-intervention" historical paid prescription claims data:

- 34 percent of hypertensive patients on Rx's increasing blood pressure;
- 45 percent of diabetic patients on Rx's raising blood sugar;
- 41 percent of ulcer patients on Rx's causing ulcers;
- 20 percent of depressed patients on Rx's causing depression.

Estimates as to the number of hospitalizations attributable to inappropriate use of prescription drugs range from 10% for the general population to 23% among the elderly.[2] Since the elderly are far more likely to be on multiple chronic care medications and are physically more susceptible to the effects of drugs, the incidence of potential drug conflicts is significantly higher in the elderly than in the general population. HID's experience in the Pennsylvania PACE program, an elderly population, indicates that on a monthly basis, 2% of the elderly have been identified as being at sufficient risk for drug-induced illness to warrant communications with their physicians. Translating this experience into the Medicare environment, we would expect to see approximately 1.3 million cases annually requiring some form of communication with the treating physician concerning apparent drug therapy problems.

HID has typically performed analysis of cost savings in conjunction with its therapeutic drug utilization programs. These analyses focus on reductions in both pharmaceutical utilization and rates of hospitalizations related to drug therapy problems. We have generally seen savings in pharmaceutical costs ranging from $90 to $140 in cases where an alert letter is directed to a physician. Concerning hospitalizations, the experience of HID with one large public health care program is illustrative:

> Monitoring 575,357 lives, annual hospitalization cost savings were estimated to be $4.9 million. The hospitalization rate for individuals without a drug therapy problem was 8.2 percent while the hospitalization rate was threefold higher (28.5 percent) for individuals with a drug therapy conflict.

HID has generally seen overall program savings in drug and hospital costs yielding about a 10 to 1 return on the annual investment in therapeutic drug utilization review. While it is impossible to predict with a high degree of accuracy the returns which might be achieved through a Medicare tDUR program, HID feels confident in suggesting that such a program would more than pay for itself through savings attributable to reductions in pharmaceutical costs and remedial care services. With Medicare Part A costs exceeding $50 billion, effective therapeutic drug utilization review could yield savings in the range of $3 to $5 billion annually, depending upon the potential risk identification rates and the average cost per admission.

* * * * * *

HID appreciates this opportunity to submit testimony and would welcome the opportunity to provide any additional information you may require in your ongoing assessment of available DUR technology and its capacity to improve quality of care for Medicare beneficiaries.

M Lee Morse

M. Lee Morse
President
Health Information Designs, Inc.

Footnotes

1. Carson JL, Strom BL, Morse ML, et al. The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. Archives of Internal Medicine. 1987: 1:85-88.

   Carson JL, Strom BL, Morse ML, et al. The relative gastrointestinal toxicity of the nonsteroidal anti-inflammatory drugs. Archives of Internal Medicine. 1987; 5:1054-1059.

   Strom BL, Carson JL, Morse ML, et al. The effect of indication on the risk of hypersensitivity reactions associated with tolemin sodium as other nonsteroidal anti-inflammatory drugs. Arthritis and Rheumatism. 1987; 10:1142-1148.

   Strom BL, Carson JL, Schinnar, Sim E., Morse ML. Allergic and/or anaphylactoid reactions associated with tolemetin sodium v. other nonsteroidal anti-inflammatory drugs. Journal of Rheumatology. 1988; 15:695-699.

   Strom BL, Tamragouri RN, Morse ML, et al. Oral contraceptives and other risk factors for gall bladder disease. Clinical Pharmacology and Therapeutics. 1986; 39: 335-341.

   Strom BL, West SL. Oral contraceptives and gall bladder disease. Clinical Pharmacology and Toxicology. 1987; 276: 71-86.

2. Grymonpre RE, Mitenko PA, Sitar DS, Aoki FY, Montgomery PR. "Drug-associated hospital admissions in older medical patients. Journal of the American Geriatric Society. Vol. 36, pg. 1092.

   Williamson J, Chopin JM. "Adverse reactions to prescribed drugs in the elderly: a multicentre investigation." Age and Ageing. May 1980. Vol 9, No.2, pg. 73.

American
Psychological
Association
Advancing psychology as a science, a profession, and as a means of promoting human welfare

May 19, 1989

The Honorable Thomas Downey
2232 Rayburn House Office Building
Washington, D.C. 20515-3202

RECEIVED
MAY 25 1989
Cong. Thomas J. Downey

Dear Congressman Downey:

The misuse and abuse of prescription drugs among our nation's elderly is a serious problem affecting 23 million older Americans, their families and many others. Adverse drug reactions result in over 243,000 hospital admissions each year, according to the HHS Inspector General who has referred to this as our nation's "other drug problem." Health care costs associated with adverse drug reactions among the elderly are estimated as high as $7 billion per year.

The elderly deserve options of nondrug therapy. Psychological interventions have proven effective when dealing with depression, sleep disorders, chronic pain and debilitating anxiety. Recognizing psychologists under Medicare (S. 100 and H.R. 774) will promote access to quality mental health care as a means to help alleviate this problem.

The American Psychological Association conducted a forum in February on the problem of overdrugging the elderly. As a result of the forum and based on widespread interest, the attached articles were generated on this issue. It is an issue that is of great importance to your constituents and deserves your consideration.

Thank you for your time and support on this critical issue.

Sincerely,

Bryant L. Welch

Bryant L. Welch, J.D., Ph.D.
Executive Director for Professional Practice
American Psychological Association

Donna M. Daley

Donna F. Daley
Director of Federal Advocacy
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Elderly Are Overdrugged, Psychologists Say

By DEBORAH MESCE 5 bill

WASHINGTON (AP) — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said yesterday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

A report earlier this month by the inspector general's office at the Department of Health and Human Services alleged widespread prescription drug problems among the elderly. The report said Americans over age 60 account for 51 percent of deaths and 39 percent of hospitalizations from drug reactions.

* * *

The psychologists' association concentrated on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

"Antipsychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience" at nursing homes, said William Simonson, associate professor of pharmacy at Oregon State University, who joined Welch at the briefing.

"The tragic scenario of a physically robust patient turning into a nonfunctional zombie after receiving antipsychotics has been played out many times," he said.

The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given antipsychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

Linda Keegan, a spokesman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."

She added, "While we recognize that psychotropic drugs have been used in the past as chemical restraints, physicians prescribing drugs to nursing home patients increasingly realize that such practices may help control behavior but they inevitably create new problems."

From 35 percent to 40 percent of prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12 percent of the population, the psychologists' group said.

* * *

The American Psychiatric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly. The association started such a program two years ago, said spokesman Dr. Harvey Ruben.

However, Ruben said it is "naive" for the psychologists to believe that many nursing home patients could be treated with alternative, nonmedical therapies. He said 60 percent to 70 percent of nursing home patients have some form of dementia and most would not benefit from behavior modification.

AARP NEWS BULLETIN April 1989

America's 'other drug problem' overwhelms thousands, experts say

By Peggy Eastman

Tens of thousands of older people are living in an "inhuman and needless" stupor induced by misuse or overuse of prescription drugs, medical experts told reporters last month.

"The problem of over-medication and mis-medication is so widespread that some people are calling this the nation's other drug problem," said Bryant Welch, executive director of professional practice at the American Psychological Association (APA).

Welch and others spoke at a forum convened by the APA to report new findings on this emerging drug problem. Speaker after speaker said that over-drugging is a major problem for older people who live both alone and in nursing homes, and for those who receive adult foster care and home health care.

APA's forum came just weeks after the release of a draft government report stating that mis-medication is a "widespread problem" among America's elderly.

The report, written by Richard P. Kusserow, inspector general of the Department of Health and Human Services, cited a "series of systemic weaknesses" throughout the drug delivery system. Among them: misdiagnoses by doctors, faulty prescriptions and improper use of drugs by patients.

Speakers at the APA forum said that the over-drugging problem stems in part from nursing home medication practices. They noted that nursing home staffers sometimes use drugs that calm or induce sleep as a "chemical restraint" to keep older patients quiet and manageable.

Some nursing homes administer the wrong kind of drugs, speakers said. In a study of one nursing home it was found that only 36 of the 221 residents receiving drugs to treat psychosis (a serious mental illness) actually had a diagnosis of psychosis.

Another research team discovered that 42 percent of Medicaid patients in a Tennessee nursing home were taking drugs to treat psychosis.

The episode was by no means unique, as a study of residents in 12 Massachusetts nursing homes vividly illustrated. Almost 20 percent of the residents were using two or more mind-affecting medications simultaneously, said Dr. Jerry Gurwitz, an instructor in medicine at Harvard Medical School's Division on Aging.

New federal regulations that tighten up on the use of drugs will ease the over-drugging in nursing homes somewhat, the experts said. But the over-drugging problem is getting worse in situations where an older person lives at home and gets little or no medical supervision, they said. Still other patients go from doctor to doctor demanding medicines they mistakenly think they need.

Speakers cited the case of an older woman living alone who was admitted to a hospital for "drugged behavior." It turned out she was taking 75 different prescription and nonprescription medications.

"This woman was going to lots of doctors and lots of pharmacies," said William Simonson, associate professor at Oregon State University's College of Pharmacy. "She was convinced that she needed all these pills to remain healthy, and she feared having them taken from her."

Another problem is that patients are sometimes put on four prescription medicines to control high blood pressure when one would do, Simonson said. And sometimes patients are put on a drug for one episode of belligerent behavior and then left on the drug long after, he added.

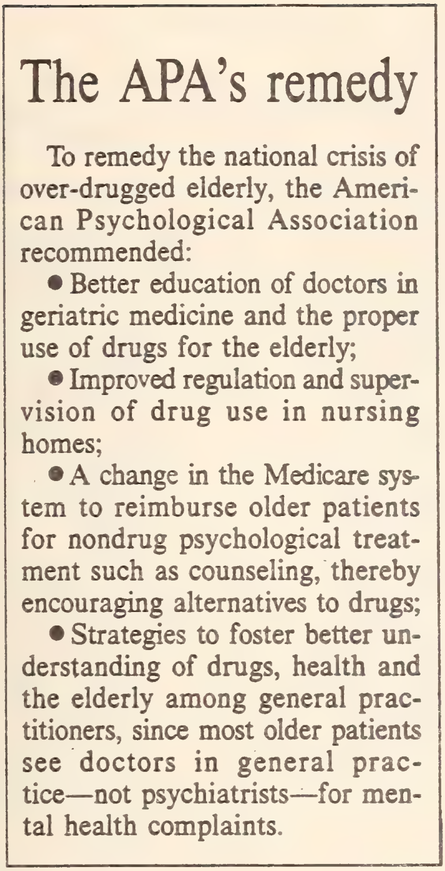
Experts at the APA forum said doctors don't conspire to drug older people. The problem is lack of knowledge, Gurwitz said. He pointed out that many doctors don't realize that as people age they become more sensitive to medicines and are more subject to over-drugging, drug interactions and adverse reactions.

Doctors may also misdiagnose drug-induced confusion or depression as a symptom of "old age," and prescribe yet another drug to treat a problem *caused* by drugs, Gurwitz said.

"While 75 percent of medical schools now have courses in geriatric medicine, less than 10 percent of medical students take them," Gurwitz estimated. And less than 2 percent of practicing doctors take continuing education courses in geriatric medicine, he added.

The consequences can be deadly. Citing the recently-released Kusserow report, the experts noted that 51 percent of deaths from drug reactions in the U.S. involve people 60 or older, even though they account for only 17 percent of the population.

Peggy Eastman is a Washington-based freelance writer.



The APA's remedy

To remedy the national crisis of over-drugged elderly, the American Psychological Association recommended:

- Better education of doctors in geriatric medicine and the proper use of drugs for the elderly;
- Improved regulation and supervision of drug use in nursing homes;
- A change in the Medicare system to reimburse older patients for nondrug psychological treatment such as counseling, thereby encouraging alternatives to drugs;
- Strategies to foster better understanding of drugs, health and the elderly among general practitioners, since most older patients see doctors in general practice—not psychiatrists—for mental health complaints.

Psychologists Say Elderly Being Excessively Medicated<

By DEBORAH MESCE=
Associated Press Writer=

WASHINGTON (AP) The nation's elderly are being ``needlessly and inhumanely'' drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are ``needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors,'' said Bryant Welch, executive director of professional practice at the association.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

A report earlier this month by the inspector general's office at the Department of Health and Human Services alleged widespread prescription drug problems among the elderly. The report said Americans over age 60 account for 51 percent of deaths and 39 percent of hospitalizations from drug reactions.

The psychologists' association concentrated on the misprescribing of psychotropic drugs medications that control behavior to older patients.

``Antipsychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience'' at nursing homes, said William Simonson, associate professor of pharmacy at Oregon State University, who joined Welch at the briefing.

``The tragic scenario of a physically robust patient turning into a nonfunctional zombie after receiving antipsychotics has been played out many times,'' he said.

The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given antipsychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug ``holidays'' when possible in an effort to discontinue use.

From 35 percent to 40 percent of prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12 percent of the population, the psychologists' group said.

The American Psychiatristric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly. The association started such a program two years ago, said spokesman Dr. Harvey Ruben.

However, Ruben said it is ``naive'' for the psychologists to believe that many nursing home patients could be treated with alternative, nonmedical therapies. He said 60 percent to 70 percent of nursing home patients have some form of dementia and most would not benefit from behavior modification.

The psychologists recommend that the Medicare program, the federal health insurance program for the elderly, be expanded to cover psychological services.

Currently, the program's mental health coverage includes services by psychiatrists, who can prescribe drugs. The services of psychologists, who are not medical doctors and cannot prescribe drugs, are not covered by Medicare.

Simonson, who specializes in geriatric pharmacology, said medications to control behavior can be used effectively to manage patients, and in nursing homes there is often pressure to use these drugs to control patients prone to wandering around, yelling or striking out at other patients.

OUTLOOK

SANTA MONICA, CA
DAILY 26,812

SATURDAY
FEB 25 1989

646 BURRELLE'S FX

Elderly need lower dosages

5608A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, non-drug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

FRESNO BEE

FRESNO, CA
DAILY 135,832

SATURDAY
FEB 25 1989

211 BURRELLE'S FX

'Inhumane' drugging of elderly charged

560SA

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday. Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, non-drug therapies such as psychological counseling, the association said in asking Medicare to cover their services. Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, an executive director at the association.

DAILY NEWS (VALLEY
EDITION)

LOS ANGELES, CA
DAILY 150,403

SATURDAY
FEB 25 1989

818 BURRELLE'S FP

Psychologists' group says elderly 'needlessly drugged'

Medicare coverage sought for alternative therapies

56C8A

By DEBORAH MESCE
Associated Press

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, non-drug therapies such as psychological counseling, the association said in asking Medicare to cover the services of its members.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

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The psychologists' association concentrated on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

"Anti-psychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience" at nursing homes, said William Simonson, associate professor of pharmacy at Oregon State University, who joined Welch at the briefing.

"The tragic scenario of a physically robust patient turning into a non-functional zombie after receiving anti-psychotics has been played out many times," he said.

The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given anti-psychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

Linda Keegan, a spokeswoman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."

She added, "While we recognize that psychotropic drugs have been used in the past as chemical restraints, physicians prescribing drugs to nursing-home patients increasingly realize that such practices may help control behavior but they inevitably create new problems."

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However, Ruben said it is "naive" for the psychologists to believe that many nursing-home patients could be treated with alternative, non-medical therapies. He said 60 percent to 70 percent of nursing-home patients have some form of dementia and most would not benefit from behavior modification.

The psychologists recommend that the Medicare program, the federal health-insurance program for the elderly, be expanded to cover psychological services.

POST-TRIBUNE
GARY, IN
DAILY [illegible]
SATURDAY
FEB 25 1989
BURRELLE'S

Psychologists say elderly are excessively medicated

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

THE BLADE
TOLEDO, OHIO
D.160,835 SUN.219,293
FEB 25 1989
BURRELLE'S

Aged overdrugged

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said yesterday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking medicare to cover their services.

From 35 percent to 40 percent of the prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12 percent of the population, the psychologists' group said.

LEXINGTON HERALD-LEADER
LEXINGTON, KY
DAILY 116,720
SATURDAY
FEB 25 1989
BURRELLE'S

Use of drugs on elderly criticized

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said yesterday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, non-drug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

ORANGE COUNTY REGISTER

SANTA ANA, CA
DAILY 307,776

SATURDAY
FEB 25 1989

BURRELLE'S
638 GF

WASHINGTON BRIEFLY

Pentagon trio's racketeering charges dropped

5608A

A federal judge in Alexandria, Va., Friday dismissed racketeering charges against three men indicted last month in the **Pentagon** procurement investigation, defense attorneys said.

While the men — two private consultants and a suspended Navy procurement specialist — no longer are accused of racketeering, they face a number of other criminal charges stemming from the Jan. 7 indictment, including bribery and theft of government property.

US District Judge Richard Williams issued his ruling from the bench and said he would file a written order next week, according to Gerard Treanor, a lawyer for William L. Parkin, a defendant.

Treanor said the judge agreed with the defense arguments that prosecutors had not presented enough evidence to satisfy racketeering charges against consultants Parkin and Fred H. Lackner, and Stuart E. Berlin, a Navy official who has been suspended without pay.

Cleanup cost revised: The cost of cleaning up radioactive and toxic waste at 16 nuclear-weapons sites in 12 states probably will exceed the official $63 billion estimate, a senior **Energy Department** official told Congress on Friday.

"It's very hard to come up with a solid estimate when you're not aware of the extent of the problem," said **Raymond R. Berube**, deputy assistant energy secretary for environment. "The more you study, the more (contamination) you find. It's a strong possibility these costs will go higher."

The Energy Department reported last month that it would cost $52 billion to modernize the weapons complex, and an additional $29 billion to clean it up over the next 21 years. The department has said the cleanup eventually would cost up to $63 billion, plus $2 billion to $4 billion for decommissioning and decontaminating parts of the complex that are permanently shut down.

Rights chief named: **Attorney General Dick Thornburgh** on Friday recommended **William Lucas**, a black lawyer and former Michigan gubernatorial candidate, to head the Justice Department's civil-rights division.

Lucas, a Republican from Detroit, ran unsuccessfully for governor in 1986. He also is a former New York City police officer, FBI agent, Wayne County, Mich., sheriff and Wayne County executive.

He worked briefly for the civil-rights division in the early 1960s, representing the Justice Department in Tuskegee, Ala., during the desegregation of the local schools, the department said.

Civil-rights advocates criticized the selection, saying Lucas lacks experience in enforcement of civil-rights laws, while conservatives applauded the choice.

Doctors criticized: The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the **American Psychological Association** said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, non-drug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said **Bryant Welch**, executive director of professional practice at the association.

Also in Washington:

■ A jury was selected Friday in the hijacking trial of Lebanese militiaman **Fawaz Younis**, a case that will test a 1984 law giving the United States jurisdiction in incidents involving US hostages abroad. In September 1987, federal agents lured Younis to a yacht in the Mediterranean Sea with the promise of a drug deal and a party, and flew him to the United States.

■ **The Department of Energy** conducted an underground nuclear-weapons test that registered less than 20 kilotons, a department spokesman said. Named the Kawich test, the underground explosion was held 1,200 feet below the surface and took place 85 miles northwest of Las Vegas. It was the department's second underground nuclear weapons-related test this year.

— From Register news services

The Kansas City Times
KANSAS CITY, MO.
D. 285,962 SAT. 314,095

FEB 25 1989
BURRELLE'S

Drugs too often prescribed to control aged, psychologists say

56034

The Associated Press

WASHINGTON — Elderly Americans are being "needlessly [illegible] inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on [illegible] to control behavior, the American Psychological Associa[illegible] said Friday.

Many of these patients could ben[illegible] from lower doses of the medications they need for chronic illnesses [illegible] from alternative, non-drug ther[illegible] such as psychological counsel[illegible] the association said in asking Medicare to cover their services.

"Too often elderly people are needlessly and inhumanely being [illegible] and psychologically abandoned to drug-induced stupors," said Bryant Welch, the association's executive director of professional practice.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

A report earlier this month by the inspector general's office at the Department of Health and Human Services alleged widespread prescription drug problems among the elderly. The report said Americans over age 60 accounted for 51 percent of deaths and 39 percent of hospitalizations from drug reactions.

The psychologists' association concentrated on the misprescribing of psychotropic drugs, medications that control behavior, to older patients.

"Anti-psychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience" at nursing homes, said William Simonson, Oregon State University associate professor of pharmacy, who joined Welch at the briefing.

The problem may be eased, he said, by Medicare regulations scheduled to go into effect later this year. The rules will require nursing homes to ensure that residents to not receive anti-psychotic drugs unless needed to treat a specific condition and that residents on the drugs have gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

Linda Keegan, a spokesman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."

She added, "While we recognize that psychotropic drugs have been used as chemical restraints, physicians prescribing drugs to nursing home patients increasingly realize that such practices may help control behavior but (that) they inevitably create new problems."

Elderly Americans, who make up about 12 percent of the population, receive from 35 percent to 40 percent of prescribed sedatives and hypnotic drugs, the psychologists' group said.

The American Psychiatric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly. The association started such a program two years ago, said spokesman Dr. Harvey Ruben.

However, Ruben said, it is "naive" for the psychologists to think that many nursing home patients could be treated with alternative, non-medical therapies. He said that 60 percent to 70 percent of nursing home patients had some form of dementia and that most would not benefit from behavior modification.

TRENTONIAN

TRENTON, NJ
DAILY 68,391

SATURDAY
FEB 25 1989
BURRELLE'S

244 XA

Report: Docs Needlessly Drugging Elderly

5608A

WASHINGTON (AP) — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said yesterday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

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"The tragic scenario of a physically robust patient turning into a nonfunctional zombie after receiving antipsychotics has been played out many times," he said.

The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given antipsychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

From 35 percent to 40 percent of prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12 percent of the population, the psychologists' group said.

The American Psychiatristric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly.

The Atlanta Journal
AND
CONSTITUTION
ATLANTA, GA.
SAT. 501,479 SUN. 645,910

FEB 25 1989
BURRELLE'S

Doctors Misusing Drugs On Elderly, Group Warns

The Associated Press 5608A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice for the association.

He spoke prior to a forum sponsored by the association's board of professional affairs on the misuse of prescription drugs for the elderly.

NEWS
PHILADELPHIA, PA.
D. 259,381 SAT. 177,900

FEB 25 1989
BURRELLE'S

Docs Drug U.S. Elderly Needlessly

Robust Patients Turned to Zombies

5608A

Associated Press

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MESA TRIBUNE

MESA, AZ
DAILY & SUNDAY 40,829

SATURDAY
FEB 25 1989

BURRELLE'S

31 KA

Psychologists: Elderly are overly medicated

By Deborah Mesce
The Associated Press 5608A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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Linda Keegan, a spokeswoman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."

THE TAMPA TRIBUNE
TAMPA, FLA.
D.218,952

FEB 25 1989

BURRELLE'S

Elderly often overmedicated 5608A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Drugging of elderly criticized

Associated Press

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However, Ruben said it is "naive" for the psychologists to believe that many nursing home patients could be treated with alternative, nonmedical therapies.

Harrisburg Patriot - News 2/26/[illegible]

Circ. morning 53,021
eve. 53,501 Sun. 170,012
other 95,002

HARRISBURG PATRIOT NEW

Press Herald, Portland, Maine 2/25/89 Circ 61,555

Psychologists say elderly being excessively medicated

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WISCONSIN STATE JOURNAL

MADISON, WI
DAILY 79,269

SATURDAY
FEB 25 1989
BURRELLE'S

132 PW

Elderly over-drugged

56C8H

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A report this month by the inspector-general's office at the Department of Health and Human Services alleges prescription drug problems among the elderly. The report says those over 60 account for 51 percent of deaths and 39 percent of hospitalizations from drug reactions.

CHICAGO DAILY CALUMET
AND POINTER

LANSING, IL
DAILY & SUNDAY 10,595

SUNDAY
FEB 26 1989
BURRELLE'S

441 TB

Drugs overused on the elderly

5603A

WASHINGTON (AP) — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, says the American Psychological Association.

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The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given antipsychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

Linda Keegan, a spokeswoman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."

Rocky Mountain News
DENVER, COLO.
D. 347,778 SUN. 379,984

FEB 25 1989
BURRELLE'S

Elderly overly medicated, U.S. psychologists say

WASHINGTON (AP) — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said yesterday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, non-drug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

A report this month by the inspector general's office at the Department of Health and Human Services described widespread prescription drug problems among the elderly. The report said Americans over age 60 account for 51% of deaths and 39% of hospitalizations from drug reactions.

The psychologists' association concentrated on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

"Anti-psychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience" at nursing homes, said William Simonson, associate professor of pharmacy at Oregon State University, who joined Welch at the briefing.

"The tragic scenario of a physically robust patient turning into a non-functional zombie after receiving anti-psychotics has been played out many times," he said.

The problem may be eased, he said, by Medicare regulations that take effect this year. The rules will require nursing homes to ensure that residents are not given anti-psychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

Linda Keegan, a spokeswoman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."

She added, "While we recognize that psychotropic drugs have been used in the past as chemical restraints, physicians prescribing drugs to nursing home patients increasingly realize that such practices may help control behavior but they inevitably create new problems."

From 35% to 40% of prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12% of the population, the psychologists' group said.

The American Psychiatristric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly. The association started such a program two years ago, said Dr. Harvey Ruben.

However, Ruben said it is "naive" for the psychologists to believe that many nursing home patients could be treated with alternative, non-medical therapies. He said 60% to 70% of nursing home patients have some form of dementia and most would not benefit from behavior modification.

SCOTTSDALE PROGRESS

SCOTTSDALE, AZ
DAILY 18,981

SATURDAY
FEB 25 1989

51 BURRELLE'S FK

Elderly are over-drugged, group says

Associated Press

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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The American Psychiatric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly.

The association started such a program two years ago, said spokesman Dr. Harvey Ruben.

TIMES TRIBUNE

PALO ALTO, CA
SAT & SUN 56,995

SATURDAY
FEB 25 1989

1003 BURRELLE'S FB

Medical group says nation's elderly being needlessly drugged

5668A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat [illegible]ic illnesses.

"Too often the elderly are "need[illegible]y and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

NATION

● More national news — D-7

Serious budget talks

WASHINGTON — Despite a week of tough questions over what critics see as big gaps in President Bush's 1990 spending plan, Budget Director Richard Darman on Friday expressed optimism that serious negotiations will soon begin with Congress over a compromise budget.

Darman predicted that in the next twoweeks the administration and congressional leaders will begin crafting a compromise budget for fiscal 1990, which begins next Oct. 1.

Cancer danger for kids

WASHINGTON — A private environmental group contends in a new report that preschool children are consuming cancer-causing chemicals in fruits and vegetables at levels that expose them to health risks many times greater than the government considers safe.

The findings by the Natural Resources Defense Council were immediately challenged by the Environmental Protection Agency, which said in a statement Friday that health risks to children are taken into account when setting allowable chemical residue levels.

AFL-CIO ends meeting

BAL HARBOUR, Fla. — AFL-CIO leaders concluded their annual winter meeting Friday with a call on Congress to make it tougher for employers to skim assets from pension funds and a vow to be a major force in the coming redrawing of congressional districts.

The federation's Executive Council also condemned a recent Treasury Department reversal of a Customs Service determination that imported multi-purpose vehicles were small trucks and therefore subject to a 25 percent import tariff.

The protracted labor dispute at Eastern Airlines dominated the weeklong meeting.

Times Tribune news services

DAILY BREEZE

TORRANCE, CA
DAILY 89,600

SATURDAY
FEB 25 1989
BURRELLE'S
702 FX.

Elderly need lower dosages

5605A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

TELEGRAPH HERALD

DUBUQUE, IA
DAILY 35,001

SATURDAY
FEB 25 1989
BURRELLE'S
940 JJ

'Needless drugs used on elderly'

5605A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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A report earlier this month by the inspector general's office at the Department of Health and Human Services alleged widespread prescription drug problems among the elderly. The report said Americans over age 60 account for 51 percent of deaths and 39 percent of hospitalizations from drug reactions.

MARIETTA DAILY JOURNAL

MARIETTA, GA
DAILY 24,649

SATURDAY
FEB 25 1989
BURRELLE'S
175 UE

Elderly being excessively medicated

5605A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

STATE

COLUMBIA, SC
DAILY 116,342

SATURDAY
FEB 25 1989
BURRELLE'S
35

Psychologists say elderly are excessively medicated

5605A

WASHINGTON

The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, non-drug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

From 35 percent to 40 percent of prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12 percent of the population, the psychologists' group said.

TEMPE DAILY NEWS TRIBUNE

TEMPE, AZ
DAILY 11,121

SATURDAY
FEB 25 1989
BURRELLE'S
60 KA

Psychologists: Elderly are overly medicate

By Deborah Mesce 5A
The Associated Press

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

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The psychologists' association concentrated on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

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"The tragic scenario of a physically robust patient turning into a nonfunctional zombie after receiving antipsychotics has been played out many times," he said.

The problem may be eased
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therapy to control behavior."

PALLADIUM-ITEM

RICHMOND, IN
DAILY 21,005

SATURDAY
FEB 25 1989
BURRELLE'S
228 TM

Elderly 'excessively medicated'

WASHINGTON The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday. Many of those patients could benefit from lower doses of medication and from nondrug therapies, such as psychological counseling, the association said in asking Medicare to cover its services.

ARIZONA REPUBLIC

PHOENIX, AZ
DAILY 343,723

SATURDAY
FEB 25 1989

BURRELLE'S
82 FK

Elderly drugged 'needlessly'

Psychologists blame doctors

The Associated Press

WASHINGTON – The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from non-drug therapies such as psychological counseling, the association said.

The elderly too often are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, the association's executive director of professional practice.

A report earlier this month by the inspector general's office of the U.S. Department of Health and Human Services alleged widespread prescription-drug problems among the elderly. The report said Americans over age 60 account for 51 percent of the deaths and 39 percent of the hospitalizations from drug reactions.

In a weeklong series last summer, *The Arizona Republic* disclosed how critical and widespread such medication abuses have become. It also revealed how poorly trained most physicians are in geriatrics.

In its report, the psychologists group concentrated on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

"Anti-psychotic drugs must be used appropriately ... not simply to control behavior, perhaps more for staff convenience" than medical need at nursing homes, said William Simonson, associate professor of pharmacy at Oregon State University.

Simonson said the problem may be eased by Medicare regulations scheduled to go into effect later this year. The rules will require nursing homes to ensure that residents are not given anti-psychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

The association said physicians need more training on prescribing psychotropic drugs for the elderly. The association started such a program two years ago, according to a spokesman, Dr. Harvey Ruben.

However, Ruben said it is "naive" for the psychologists to think that many nursing-home patients could be treated with non-medical therapies.

NATION'S HEALTH

WASHINGTON, DC
10-TIMES/YEAR 31,000

APRIL 1989
BURRELLE'S
-4692 MX

Psychologists Association Decries Improper Medication of Elderly

5608A

"The prescription of unnecessary or improper drugs for elderly patients reflects our society's psychological abandonment of a remarkable generation of Americans who could, through just a little more effort, be helped to live out their years with the dignity and respect they deserve," said Bryant Welch, JD, PhD, executive director of professional practice at the American Psychological Association (APA).

The APA held a forum and issued a statement recently to call for steps to curb the overuse and misuse of drugs for the elderly, particularly those drugs used to treat mental disorders.

The APA forum followed a report from the Department of Health and Human Services Inspector General which found a severe problem of mismedication among elderly adults.

The elderly in general do not have higher rates of mental disorders, other than organic related cognitive impairments, than any other adult age group, according to Meyer D. Glantz, PhD, of the National Institute on Drug Abuse. And, yet, he said, the elderly account for about one third of the prescribed psychotherapeutics, with the disproportionate use being even greater in elderly women.

On the other hand, the elderly are the least likely group to be treated by mental health professionals and the least likely to receive psychotherapy, according to Glanz.

"General medical sector physicians frequently serve as gatekeepers to the mental health sector. These physicians and the elderly themselves often think of older adults as being inappropriate and unsuccessful psychotherapy candidates," he said.

Psychotropic drug use has been associated with some of the major health problems of the elderly, including falls, hip fractures, cognitive impairment and incontinence, said APA. Further, said the group, there is growing evidence that "an important proportion" of these problems may be due to drugs that were inappropriately prescribed.

The greatest problem with misuse of antipsychotic medications seems to be in institutionalized elderly, APA said.

However, problems with all types of drugs, according to forum participants, include pressure on physicians from elderly patients to get medications they want, use of multiple medications, drug interactions, and adverse drug reactions which often go undiagnosed in the elderly.

APA recommended that training of general care physicians in the proper use of drugs for the elderly be mandated; that regulation and supervision of drug use in nursing homes and similar facilities be improved; that Medicare be changed to reimburse patients for psychological treatment; and that a better understanding of mental health and the elderly be promoted among health care practitioners.

ANN ARBOR NEWS

ANN ARBOR, MI
DAILY 49,819

TUESDAY
MAR 7 1989
BURRELLE'S

9 RE

Elderly suffering mental ills without hope of aid

5744A

JULIE JOHNSON
THE NEW YORK TIMES

WASHINGTON — Many of the elderly have mental health problems requiring some form of help but are not getting any, a congressional panel was told.

"While nearly 7 million elderly need some type of mental health assistance, only a few are receiving that help," Sen. John D. Rockefeller IV, a West Virginia Democrat who has introduced legislation that would extend reimbursement to psychologists under Medicare. Federal insurance for the elderly pays now only for treatment provided by psychiatrists and other medical doctors.

Rockefeller, testifying before the House Ways and Means Health Subcommittee, said the elderly receive "less mental health care" than any other age group.

"As many as 80 percent are not receiving the care they need," he said. "Without appropriate care many seniors are forced to live unnecessarily unhappy, confused, or institutionalized lives."

Researchers at the National Institute of Mental Health and National Institute on Aging were interviewed about these and other assertions. "The magnitude of the problem is significant," said Dr. Gene D. Cohen, a geriatric psychiatrist who is deputy director of the National Institute of Aging.

In addition, Cohen said, older adults have a number of "physical disorders that lower the threshold to depression."

"Also," he went on, "there are medications that are used to treat a number of conditions, among them cardiac conditions, that have a higher risk of depression as a side effect."

As Americans live longer, mental health professionals have sought to broaden therapeutic approaches to older patients, a grouping generally viewed as difficult, according to experts at the National Institute of Mental Health and the National Institute on Aging.

Barry D. Lebowitz, chief of the National Institute of Mental Health's research branch in mental disorders of the aging, said psychotherapy focuses on the young, attractive, verbal, intelligent, and sophisticated, a group known in the helping professions as Yavias, like yuppies. Beyond that, other factors restrict the provision of mental health services to the elderly, he said.

Medicare, the federal health insurance plan for the elderly, has only recently broadened its reimbursement criteria for mental health care, but providing treatment is still limited largely to physicians or psychiatrists. In some cases, however, reimbursing does cover treatment by psychologists in rural health clinics and mental health centers.

Reimbursement restrictions under Medicare are compounded, Lebowitz said, by the "relatively small number" of professionals are trained to treat the elderly, that services often are not widely accessible to the elderly and that stigmas still exist among older people about seeking treatment for depression, grief, or loneliness.

On the basis of a survey of 645 community mental health centers, the National Institutes of Mental Health estimated that 10.5 percent of the cases were patients aged 60 or older, Lebowitz said. The survey was conducted in 1982-83 and again in 1983-84 in Durham, N.C., New Haven, Conn., Los Angeles, St. Louis, and East Baltimore, Md. The research was conducted by Duke University, Yale University, the University of California at Los Angeles, and Johns Hopkins.

"There are people who don't use the services," said Lebowitz. "Should people get the services? Yes. Is there room for mental health interventions with older people? Yes."

Psychologists support the bill to expand Medicare quoting an estimate by the Congressional Budget Office that it would cost only about $10 million a year to do so.

Also, Bryant Welch, the American Psychological Association's director of professional practice, asserted that widespread problems of mis-medicating of the elderly bolster arguments that therapies that do not use drugs should be more widely used, particularly among older patients.

Welch, a lawyer with a doctorate in clinical psychology, said that among the elderly, 15 percent suffer from depression, 7 percent to 10 percent suffer from anxiety disorders, and about 5 percent suffer from a cognitive impairment.

While these disorders can be widely observed among younger people as well, Welch asserted that among the elderly they are compounded routinely by stresses associated with retirement, the deaths of spouses or loved ones, and the loss of mobility or activity that is associated with the physical impairments of aging.

[illegible]
DAILY [illegible]

SATURDAY
FEB 25 1989
BURRELLE'S

12 FL

Elderly receive too much medication, group says

5U08A 1

WASHINGTON (AP) — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said yesterday.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

A report earlier this month by the inspector general's office at the Department of Health and Human Services alleged widespread prescription drug problems among the elderly. The report said Americans over age 60 account for 51 percent of deaths and 39 percent of hospitalizations from drug reactions.

The psychologists' association concentrated on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

"Antipsychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience" at nursing homes, said William Simonson, associate professor of pharmacy at Oregon State University, who joined Welch at the briefing.

"The tragic scenario of a physically robust patient turning into a nonfunctional zombie after receiving antipsychotics has been played out many times," he said.

The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given antipsychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

From 35 percent to 40 percent of prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12 percent of the population, the psychologists' group said.

The American Psychiatristric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly. The association started such a program two years ago, said spokesman Dr. Harvey Ruben.

However, Ruben said it is "naive" for the psychologists to believe that many nursing home patients could be treated with alternative, nonmedical therapies. He said 60 percent to 70 percent of nursing home patients have some form of dementia and most would not benefit from behavior modification.

The psychologists recommend that the Medicare program, the federal health insurance program for the elderly, be expanded to cover psychological services.

Currently, the program's mental health coverage includes services by psychiatrists, who can prescribe drugs. The services of psychologists, who are not medical doctors and cannot prescribe drugs, are not covered by Medicare.

COURIER-NEWS

BRIDGEWATER, NJ
DAILY 52,000

SATURDAY
FEB 25 1989
BURRELLE'S
662 XG

High medication levels for elderly criticized

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said yesterday.

HERALD

EVERETT, WA
DAILY 56,898

SATURDAY
FEB 25 1989

59 BURRELLE'S HC

Elderly suffer over-medication, psychologists say

Associated Press 5603A

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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St. Petersburg Times
ST. PETERSBURG, FLA.
D. 285,549 SUN. 350,400

FEB 25 1989
BURRELLE'S

Elderly in U.S. over-drugged, group asserts

Associated Press 56058A

WASHINGTON — Many of the nation's elderly are being "needlessly and inhumanely" medicated by doctors who rely on drugs to control behavior, the American Psychological Association said Friday.

Many of these patients could benefit from lower doses of the medications and from alternative therapies such as psychological counseling, the association said.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

The group held a forum on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

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The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given anti-psychotic drugs unless needed to treat a specific condition.

DAILY PRESS &
TIMES-HERALD

NEWPORT NEWS, VA
SATURDAY 4,357

FEB 25 1989
BURRELLE'S
169

Elderly 'needlessly' drugged

56058A

WASHINGTON (AP) — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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The Oregonian
PORTLAND, OREGON
D. 321,677 SAT. 312,448
SUN 404,186

FEB 25 1989
BURRELLE'S

Psychologists fret over drugs

560EP

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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The Cincinnati Post
CINCINNATI, OHIO
D. 115,718

FEB 25 1989
BURRELLE'S

Psychologists group decries drugging of older patients

5608A

Associated Press

WASHINGTON — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, the American Psychological Association said Friday.

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The Nation's Health

april 1989 THE OFFICIAL NEWSPAPER OF THE AMERICAN PUBLIC HEALTH ASSOCIATION ISSN: 0028-0496

Psychologists Association Decries Improper Medication of Elderly

"The prescription of unnecessary or improper drugs for elderly patients reflects our society's psychological abandonment of a remarkable generation of Americans who could, through just a little more effort, be helped to live out their years with the dignity and respect they deserve," said Bryant Welch, JD, PhD, executive director of professional practice at the American Psychological Association (APA).

The APA held a forum and issued a statement recently to call for steps to curb the overuse and misuse of drugs for the elderly, particularly those drugs used to treat mental disorders.

The APA forum followed a report from the Department of Health and Human Services Inspector General which found a severe problem of mismedication among elderly adults.

The elderly in general do not have higher rates of mental disorders, other than organic related cognitive impairments, than any other adult age group, according to Meyer D. Glantz, PhD, of the National Institute on Drug Abuse. And, yet, he said, the elderly account for about one third of the prescribed psychotherapeutics, with the disproportionate use being even greater in elderly women.

On the other hand, the elderly are the least likely group to be treated by mental health professionals and the least likely to receive psychotherapy, according to Glanz.

"General medical sector physicians frequently serve as gatekeepers to the mental health sector. These physicians and the elderly themselves often think of older adults as being inappropriate and unsuccessful psychotherapy candidates," he said.

Psychotropic drug use has been associated with some of the major health problems of the elderly, including falls, hip fractures, cognitive impairment and incontinence, said APA. Further, said the group, there is growing evidence that "an important proportion" of these problems may be due to drugs that were inappropriately prescribed.

The greatest problem with misuse of antipsychotic medications seems to be in institutionalized elderly, APA said.

However, problems with all types of drugs, according to forum participants, include pressure on physicians from elderly patients to get medications they want, use of multiple medications, drug interactions, and adverse drug reactions which often go undiagnosed in the elderly.

APA recommended that training of general care physicians in the proper use of drugs for the elderly be mandated; that regulation and supervision of drug use in nursing homes and similar facilities be improved; that Medicare be changed to reimburse patients for psychological treatment; and that a better understanding of mental health and the elderly be promoted among health care practitioners.

March 6, 1989

HEALTHWEEK

The Newspaper For America's Health Industry

A CMP Publication

Overmedication, the elderly

• Legislation to broaden Medicare coverage for psychiatric services would help solve the problem of overmedication among the elderly, officials from the American Psychological Association said earlier this month after the Department of Health and Human Services released a report on the issue.

Some doctors use drugs to treat mental problems in the elderly that could be addressed without medication, the officials said.

Medicare currently covers only psychiatric services provided by physicians. Legislation introduced earlier this month by Rep. William Coyne, D-Penn., would expand coverage to psychologist's services. The House Ways and Means Committee's health subcommittee will hold a hearing on the bill today. □

WASHINGTON *Report*

Prescription errors haunt elderly—report

Mistakes by physicians, misguided government policies and other factors are causing widespread and sometimes fatal problems for elderly persons who use prescription drugs, a government study says.

About 243,000 older Americans were hospitalized in 1985 after suffering adverse reaction to drugs, said the report, released last week by the Dept. of Health and Human Services' inspector general's office. While people older than 60 represent 17% of the population, they accounted for 39% of the hospitalizations and 51% of the deaths from adverse drug reactions, the inspector general's report said.

There are several reasons why older adults are prone to improper medication, the report said. For example, young adults typically are used as test subjects in clinical studies conducted to gain drug approvals from the Food and Drug Administration, even when the products will be used primarily by elderly persons.

In addition, the report found many instances of physicians writing inappropriate prescriptions for elderly patients. These mistakes stemmed from inadequate training in geriatric medicine, the report said.

To correct these problems before 1991, when Medicare's prescription drug benefit will go into effect, the federal government should design a utilization review program directed at pharmacists, fiscal intermediaries and physicians, it said.

—CAPITAL DIGEST—

AHA OPPOSES PHYSICIAN OWNERSHIP BILL. The American Hospital Assn. is opposing legislation sponsored by Rep. Fortney "Pete" Stark (D-Calif.), that would stop Medicare payments to physicians who refer patients to health facilities in which they have an ownership interest. The AHA's board of trustees said while some ownership deals cause a conflict of interest, the proposal needs a fair process for determining legitimate exceptions.

BILLS WOULD BOOST FAMILY PLANNING FUNDS. Two leading health policymakers on Capitol Hill have introduced measures to reauthorize family health planning measures for the next four years. Rep. Henry A. Waxman (D-Calif.) seeks a funding boost for basic family planning services to $156 million in fiscal 1990 and $181 million in fiscal 1993. Fiscal 1989 spending is set at $135 million. Companion legislation is sponsored by Sen. Edward M. Kennedy (D-Mass.).

FRIENDS, FAMILY PROVIDE MOST CARE—STUDY. Most care for dependent senior citizens is provided free by friends and family, a General Accounting Office report indicates. The study found that 6.2 million to 6.5 million Americans in 1985 were dependent on others for help with basic activities, such as eating, dressing and bathing. About 80% of the dependent elderly lived in the community and received care there, the GAO reported.

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Drugs overused on the elderly

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WASHINGTON (AP) — The nation's elderly are being "needlessly and inhumanely" drugged by doctors who are inexperienced in treating older patients and who rely on drugs to control behavior, says the American Psychological Association.

Many of these patients could benefit from lower doses of the medications they need to treat chronic illnesses and from alternative, nondrug therapies such as psychological counseling, the association said in asking Medicare to cover their services.

Too often the elderly are "needlessly and inhumanely being left and psychologically abandoned to drug-induced stupors," said Bryant Welch, executive director of professional practice at the association.

He spoke to reporters at a briefing in advance of a forum sponsored by the association's board of professional affairs on the overuse and misuse of prescription drugs for the elderly.

A report earlier this month by the inspector general's office at the Department of Health and Human Services alleged widespread prescription drug problems among the elderly. The report said Americans over age 60 account for 51 percent of deaths and 39 percent of hospitalizations from drug reactions.

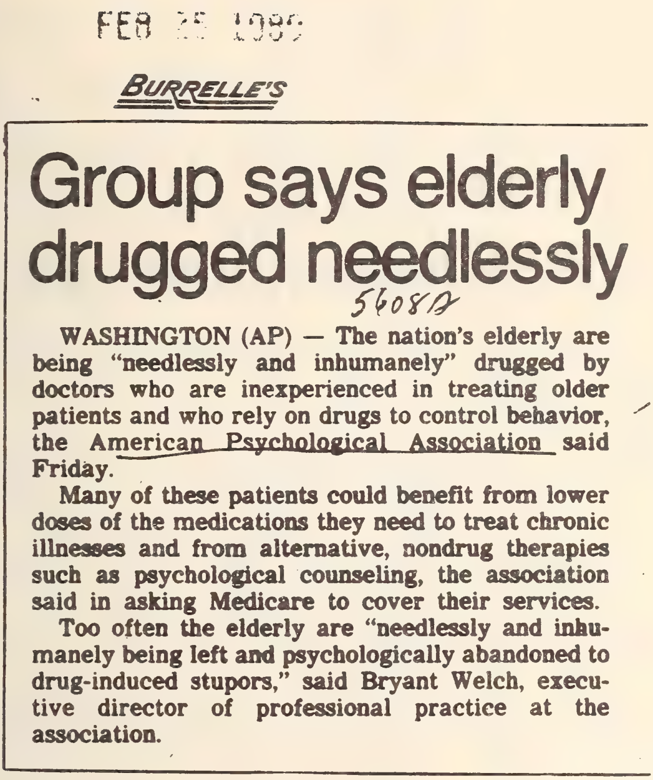
The psychologists' association concentrated on the misprescribing of psychotropic drugs — medications that control behavior — to older patients.

"Antipsychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience" at nursing homes, said William Simonson, associate professor of pharmacy at Oregon State University, who joined Welch at the briefing.

"The tragic scenario of a physically robust patient turning into a nonfunctional zombie after receiving antipsychotics has been played out many times," he said.

The problem may be eased, he said, by Medicare regulations due to go into effect later this year. The rules will require nursing homes to ensure that residents are not given antipsychotic drugs unless needed to treat a specific condition and that residents who use the drugs be given gradual dose reductions or drug "holidays" when possible in an effort to discontinue use.

Linda Keegan, a spokeswoman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."



FEB 25 1989

BURRELLE'S

Group says elderly drugged needlessly

5608B

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Psychologists Say Elderly Are Being Excessively Medicated

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Linda Keegan, a spokeswoman for the American Health Care Association, which represents more than 8,000 nursing homes, noted that "government standards for care currently discourage the use of drug therapy to control behavior."

She added, "While we recognize that psychotropic drugs have been used in the past as chemical restraints, physicians prescribing drugs to nursing home patients increasingly realize that such practices may help control behavior but they inevitably create new problems."

From 35 percent to 40 percent of prescribed sedatives and hypnotic drugs go to elderly Americans, who make up about 12 percent of the population, the psychologists' group said.

The American Psychiatric Association agrees that physicians need more training about prescribing psychotropic drugs for the elderly. The association started such a program two years ago, said spokesman Dr. Harvey Ruben.

However, Ruben said it is "naive" for the psychologists to believe that many nursing home patients could be treated with alternative, nonmedical therapies. He said 60 percent to 70 percent of nursing home patients have some form of dementia and most would not benefit from behavior modification.

The psychologists recommend that the Medicare program, the federal health insurance program for the elderly, be expanded to cover psychological services.

Currently, the program's mental health coverage includes services by psychiatrists, who can prescribe drugs. The services of psychologists, who are not medical doctors and cannot prescribe drugs, are not covered by Medicare.

Simonson, who specializes in geriatric pharmacology, said medications to control behavior can be used effectively to manage patients, and in nursing homes there is often pressure to use these drugs to control patients prone to wandering around, yelling or striking out at other patients.

PSYCHOLOGISTS CALL FOR CURBS ON OVER-DRUGGING SENIORS

The American Psychological Association (APA), citing a recently-released draft report on drugs and the elderly, last week called for steps to curb overuse and misuse of prescription drugs for elderly Americans, particularly those used to treat mental illness.

Recommendations made by APA to combat the problem include improving regulation of drug use in nursing homes, mandating geriatric care training for physicians and altering the Medicare system to allow for reimbursement of psychological services.

The report that served as the impetus for the APA recommendations was released last month by the Inspector General of the Department of Health and Human Services (HHS), Richard Kusserow. It said the problem of mismedication is so widespread that some are calling it "the nation's other drug problem." Kusserow recommended that before the 1992 phase-in of Medicare prescription drug benefits, the Health Care Financing Administration (HCFA) implement a Drug Utilization Review (DUR) system to monitor the drug consumption of the Medicare population. Without such a system, he said, the drug benefits could lead to the "over-narcotizing" of older Americans.

Elderly Purchase Greater Share of Prescription Drugs

Statistics show that while elderly Americans comprise about 12% of the U.S. population, they purchase 25-30% of all prescription drugs and 35-40% of sedative-hypnotic drugs. A 1988 Harvard study of patients in 12 intermediate-care facilities in Massachusetts called for improvement in the use of psychoactive drugs in elderly patients after concluding the drugs were overused.

"Antipsychotic drugs must be used appropriately, for specific documentable reasons, not simply to control behavior, perhaps more for staff convenience than for the benefit of the patient," said William Simonson, professor of pharmacy practice, during an APA-sponsored news conference Feb. 24. "Occasionally, these drugs are used to treat behaviors that might be more appropriately addressed by non-drug interventions, such as behavior modification."

Simonson, of Oregon State University, later repeated his warnings at a forum sponsored by APA's Board of Professional Affairs. Also addressing the topic of "drugging the elderly" were Jerry Gurwitz, M.D., of Harvard Medical School Division on Aging, and Meyer Glantz, Ph.D., of the National Institute on Drug Abuse. Glantz, a clinical psychologist, attributed much of the over-drugging problem to stereotypes about the elderly that encourage drug treatment rather than non-drug therapy.

To address the problem, the APA and forum participants called for Medicare reimbursement for psychological treatment "thus permitting alternatives to drug therapy for behavioral and psychological problems for those elderly who want such alternatives." Currently, only physicians (psychiatrists) are reimbursed by Medicare for mental health treatment. Legislation to alter the Medicare program to allow payments to psychologists was introduced in both the Senate and the House in February (H.R. 774, S. 100). A Ways and Means Committee hearing on the House bill is scheduled for March 6.

The American Psychiatric Association, which will testify at the hearing, opposes the legislation, saying psychologists are seeking authority to begin prescribing medications themselves.

(Continued)

DRUGGING THE ELDERLY (Continued)

In introducing his measure, Coyne noted that many private and federal health carriers already cover psychologists' services. The legislation is supported by several groups, including the National Association of State Mental Health Program Directors.

Forum participants also called for improved regulation and supervision of drug use in nursing homes and similar facilities. HCFA has already taken a "giant step" toward this goal in proposing regulations last month designed to encourage the proper use of antipsychotic medications in the nursing home environments, they said. The proposal, published in the Feb. 2 Federal Register, says nursing facilities must ensure that:

- "Residents who have not used antipsychotic drugs are not given these drugs unless antipsychotic drug therapy is necessary to treat a specific condition; and

- Residents who use antipsychotic drugs receive gradual dose reductions, drug holidays or behavioral programming, unless clinically contraindicated in an effort to discontinue these drugs."

LETTER BLASTS VA FOR ELIMINATING ALCOHOL, DRUG TREATMENT PROGRAMS

Attempts by the Veterans Administration to eliminate some alcohol and drug treatment programs because of budget constraints have evoked outcries from mental health and alcohol treatment groups.

Members of a mental health liaison group that meets monthly in Washington, D.C., at the American Psychiatric Association headquarters have drafted a letter to Sen. Alan Cranston (D-Calif.), chairman of the Senate Veterans Affairs Committee, asking for his help. In addition, the National Advisory Council on Alcohol Abuse and Alcoholism (NACAAA) has issued a resolution condemning the VA's actions.

Already the VA has eliminated programs at eight facilities across the country, "an action which has closed 4,300 inpatient beds, ended outpatient treatment for more than 8,600 veterans and forced four universities to dissaffiliate their mental health services from VA hospitals," says the letter. The groups charged that the VA is acting irresponsibly by restricting access to care when current needs have never been met. "It is imperative that the VA be held accountable for their ongoing efforts to reduce the availability of care and directed to find a long-range fiscal solution which does not threaten to futher deteriorate the quality of care afforded veterans," the letter adds.

Groups endorsing the letter sent by the liaison group include the American Psychiatric Association, the American Psychological Association and the Mental Health Law Project.

NACAAA, in its resolution, charges the VA with implementing a short-sighted response to the present fiscal crisis. "The use of eligibility rules to prevent alcoholics from obtaining needed treatment and the elimination of alcoholism treatment programs will cause an increased burden on public sector alcohol programs, as well as an increase in the prevalence of serious medical consequences of alcoholism among patients who will return to VA medical services at a greater cost," the resolution states.

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BURRELLE'S

Mental Ills of Elderly Need Help, Panel Told

5668A

By JULIE JOHNSON

Special to The New York Times

WASHINGTON, March 6 — Many of the elderly have mental health problems requiring some form of help but are not getting any, a Congressional panel was told today.

"While nearly 7 million elderly need some type of mental health assistance, only a few are receiving that help," said Senator John D. Rockefeller 4th, a West Virginia Democrat who has introduced legislation that would extend reimbursement to psychologists under Medicare. Federal insurance for the elderly pays now only for treatment provided by psychiatrists and other medical doctors.

Mr. Rockefeller told the House Ways and Means Health Subcommittee that the elderly receive "less mental health care" than any other age group.

"As many as 80 percent are not receiving the care they need," he said. "Without appropriate care many seniors are forced to live unnecessarily unhappy, confused, or institutionalized lives."

Researchers at the National Institute of Mental Health and National Institute on Aging were interviewed about these and other assertions. "The magnitude of the problem is significant," said Dr. Gene D. Cohen, director of the National Institute of Aging.

In addition, he said, older adults have a number of "physical disorders that lower the threshhold to depression."

"Also," he went on, "there are medications that are used to treat a number of conditions, among them cardiac conditions, that have a higher risk of depression as a side effect."

Barry D. Lebowitz, chief of the National Institute of Mental Health's research branch in mental disorders of the aging, said psychotherapy focuses on the young, attractive, verbal, intelligent and sophisticated.

Medicare, the Federal health insurance plan for the elderly, only recently broadened its reimbursement criteria for mental health care, but providing treatment is still limited largely to physicians or psychiatrists.

Reimbursement restrictions under Medicare are compounded, Mr. Lebowitz said, by the "relatively small number" of professionals trained to treat the elderly.

On the basis of a survey of 645 community mental health centers, the National Institutes of Mental Health estimated that 10.5 percent of the cases were patients aged 60 or older, Mr. Lebowitz said. The survey was conducted in 1982-83 and again in 1983-84 in Durham, N.C., New Haven, Los Angeles, St. Louis and East Baltimore, Md. The research was conducted by Duke University, Yale University, the University of California at Los Angeles, and Johns Hopkins.

Psychologists support the bill to expand Medicare quoting an estimate by the Congressional Budget Office that it would cost only about $10 million a year to do so.

Bryant Welch, the American Psychological Association's ~~director of professional practice~~, said widespread problems of mis-medicating of the elderly bolster arguments that therapies that do not use drugs should be more widely used.

Mr. Welch, a lawyer with a doctorate in clinical psychology, said that among the elderly, 15 percent suffer from depression, 7 to 10 percent suffer from anxiety disorders and about 5 percent suffer from a cognitive impairment.

He said these disorders are compounded by stresses associated with retirement, the deaths of spouses or loved ones and loss of mobility or activity.

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BURRELLE'S

Elderly Suffer Mental Ills Without Hope of Aid, Congress Panel Told

By JULIE JOHNSON

Special to The New York Times

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"While nearly 7 million elderly need some type of mental health assistance, only a few are receiving that help," Senator John D. Rockefeller 4th, a West Virginia Democrat, told the House Ways and Means Health Subcommittee. He has introduced legislation that would extend reimbursement to psychologists under Medicare. Federal insurance for the elderly pays now only for treatment provided by psychiatrists and other medical doctors.

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He said these disorders are compounded by stresses associated with retirement, deaths of spouses or loved ones and loss of mobility.

These estimates do not include older adults with Alzheimer's disease, between 5 and 6 percent, according to th National Institutes of Mental Health major depression, between 1 and 2 pe cent, and psychoses not related to Al heimer's, less than 1 percent.

Dr. Melvin Sabshin, the psycholog cal association's medical directo said, "Psychologists are not capable making" an assessment of biologic or biochemically based illness.

Representative Jim McDermott, Democrat of Washington who is a ps chiatrist, proposed that the law cou require that a medical diagnosis made by a physician before treatme was begun.

AMERICAN MEDICAL NEWS

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Psychiatry, psychology spokesmen at hearing

Issue of Medicare pay for psychologists sparks debate

By Charles Culhane 56087
AMN STAFF

Should Medicare reimburse clinical psychologists for mental health care services if the patient has not been referred by a physician? Spokesmen for psychiatrists and psychologists, testifying at a congressional hearing, sharply disagreed.

They clashed during testimony on HR 774, a bill sponsored by Rep. William J. Coyne (D, Pa.), that would permit direct Medicare reimbursement for the services of psychologists. Sen. Jay Rockefeller (D, W.Va.), has introduced a similar measure (S 100) in the Senate.

An official of the American Psychiatric Assn. urged Congress to amend the proposed legislation to require a finding that mental health treatment of a Medicare patient is medically necessary and appropriate. "To achieve that objective we urge, as a condition precedent, that there be a medical differential diagnosis and a treatment plan by a physician, preferably a psychiatrist, before reimbursement to psychologists for mental health treatment," said Melvin Sabshin, MD, medical director of the psychiatric association.

But a spokesman for clinical psychologists disagreed. "Data indicate that psychiatrists misdiagnose 50% of the major medical illnesses they see," said Bryant Welch, PhD, executive director for professional practice of the American Psychological Assn. "Psychiatry's insistence on medical referral for psychological care would set the cat among the pigeons."

Although many private insurance carriers cover the mental health services that psychologists provide, under current law the Medicare program covers such treatment only if psychologists provide the services in community mental health centers, in rural health clinics, or under the direct supervision of a physician.

"The prevalence of mental disorders in the elderly is well documented," said Rep. Fortney "Pete" Stark (D, Calif.), who chairs the House Ways and Means Committee Subcommittee on Health, which convened the hearing.

"Purely psychological problems, such as depression, grief, or loneliness, are often compounded by organic disorders, such as Alzheimer's disease," Stark said. Numerous studies show that older people often fail to get effective treatment for mental health problems, he said.

EXISTING MEDICARE regulations sharply limit reimbursement to psychologists for mental health services, Stark noted.

"Psychologists could play a more active role in providing care to our elderly and disabled if this restrictive policy were amended," he added.

Dr. Sabshin objected strongly to the idea that psychiatrists and psychologists are competing providers of services for mental disorders. "They emphatically are not comparable," he said.

While psychologists and other mental health providers such as social workers and psychiatric nurses are trained to perform psychotherapy, they are not trained, as psychiatrists are, to provide medical diagnosis and treatment to patients, Dr. Sabshin said.

"Often Medicare patients have more than one physical disorder and their multiple comorbidities may be further exacerbated by the interaction of the many medications they take," he said. "The medical differential diagnosis of the Medicare patient is a complex one requiring the expertise of physicians."

Dr. Sabshin said that many physical diseases present as psychiatric illnesses. These include endocrine problems such as hypothyroidism and neurological diseases such as myasthenia gravis, Alzheimer's disease, multiple sclerosis, brain tumors, pancreatic carcinoma, and electrolyte and fluid imbalances.

"Evidence also suggests that certain medicines such as beta blockers for high blood pressure may cause severe depression, and the treatment is really a change in the medicine or dosage," Dr. Sabshin said.

"Treating the symptoms of a disorder may thus be costly for patient care and may result in inadequate quality of care for patients," Dr. Sabshin added.

He said that when psychiatrists are not available, other physicians should provide the patient's mental illness differential diagnosis and treatment plan. "Psychologists are not capable of making this differential medical diagnosis," he said.

'Psychiatry and psychology are not interchangeable disciplines. They are complementary disciplines which may at times use similar psychotherapeutic procedures.'
Melvin Sabshin, MD

"Psychiatry and psychology are not interchangeable disciplines. They are complementary disciplines which may at times use similar psychotherapeutic procedures."

Dr. Sabshin said that psychologists make a psychological diagnosis and treat patients with psychological techniques only. "They [the psychologists] allege that where medical treatment is needed they will, in good conduct, practice, and ethics, request medical assistance. But psychologists are not trained to determine that medical assistance is needed."

'. . . Poor access to a very limited pool of Medicare-eligible psychiatrists contributes significantly to the elderly not receiving the mental health services they need.'
Bryant Welch, PhD

Stark told Dr. Sabshin that about two-thirds of all Medicare beneficiaries already see physicians on a regular basis. "So it is a matter of indifference whether they might also see a psychiatrist or a psychologist for a specific mental health problem. They already have a differential medical diagnosis."

A member of Congress who also is a psychiatrist supported Dr. Sabshin's proposal urging a requirement in the legislation for a medical differential diagnosis. Elderly people may experience emotional or mental symptoms caused by medical illnesses alone or as a result of both physical illness and the stress of life, said Rep. James McDermott, MD, a Democrat from Seattle, who has practiced more than 20 years as a psychiatrist there.

"In order to give quality care for the symptoms of depression, a differential diagnosis and treatment plan must be developed," he said. "Medical training is required to make such a diagnosis, and, for that reason, there should be a required medical differential diagnosis before treatment is begun."

But Dr. Welch, speaking for clinical psychologists, said that physicians with little knowledge of mental health problems, not psychiatrists, often provide mental health care services to the elderly. "Shockingly, between 75% and 85% of all mental health services received [by older people] do not come from a mental health professional but, instead, are rendered by general physicians who typically have less than three months of mental health training and are poorly equipped to detect, diagnose, or to treat the mental health needs of the elderly," he noted.

Dr. Welch said that about one-fourth of the 23 million U.S. elderly have a disorder that requires mental health care. "Indeed, to grow old is to suffer loss — loss of loved ones, loss of bodily functioning, loss of familiar surroundings, and oftentimes loss of hope for the future. The prevalence of depression, suicide, cognitive impairment, disorientation, anxiety, disorders, and a variety of other behavioral disorders are commonplace with our nation's elderly."

Dr. Welch contended that medical practitioners tend to overuse psychoactive drugs for the psychological needs of older people. "Elderly Americans comprise approximately 12% of the U.S. population but purchase 35% to 40% of the sedative-hypnotic drugs sold in this country. . . ."

Fewer than 25% of the elderly who need mental health care actually see a qualified mental health care professional, Dr. Welch added. "It is a simple fact that poor access to a very limited pool of Medicare-eligible psychiatrists contributes significantly to the elderly not receiving the mental health services they need.

"It also contributes to the problem of inappropriate treatment or mistreatment by forcing the elderly to bring their mental health complaint to more accessible primary care physicians who generally are not trained in mental health care and either misdiagnose the problems or prescribe harmful and inappropriate treatment."

Dr. Welch said that stress, depression, uncontrollable anxiety, and sleeplessness are common conditions among the elderly. "Older patients with these disorders are often run through an exhaustive list of diagnostic medical tests, lab work, or x-rays. Meanwhile, medical bills are increasing and the mental health disorder continues to go undiagnosed and untreated."

He said that both mental and physical health then deteriorate and physicians often prescribe some kind of drug therapy that then leads to a new set of disorders caused by the medication.

Dr. Welch said that increasingly intense pressure on health care costs inevitably will intensify competition among practitioners of various kinds. "However, we believe it is more humane to reduce costs through competition than it is to arbitrarily deny access to those elderly who would like to use a psychologist's services and to force them, instead, to rely on the present antiquated structure."

ANOTHER SPOKESMAN for the psychologists said that passage of HR 774 would nearly double the access that older people have to mental health services across the nation. "In California, this could mean that seniors will have access to care by 8,000 psychologists to which they are denied access at present," said Nicholas Cummings, PhD, a past president of the American Psychological Assn.

Dr. Cummings contended that older people are receiving relatively good medical care from the Medicare program but receive little or no mental health care. "The real issue is how to ensure that the elderly get more appropriate mental health care. The general physicians provide the bulk of mental health care and are barriers to appropriate mental health services."

He cited the case of a 79-year-old woman whose diagnosis was Alzheimer's disease. "Upon psychological evaluation she was found to be taking 28 different medications, seven of them prescribed by several psychiatrists."

Cummings said that a psychologist performed an evaluation and asked for a thorough medical evaluation of the patient. "The psychologist had the patient removed from all medications except three. Within two weeks, there were no symptoms of senility, and she was, in every respect, sound."

ROCKEFELLER told the subcommittee that the elderly receive less mental health care than any other age group. "While nearly 7 million elderly need some type of mental health assistance, only a few are receiving that help. As many as 80% are not receiving the care they need.

"I believe Medicare coverage of psychologists' services will go a long way toward meeting the elderly's tremendous need for mental health services. . . . Without appropriate care, many seniors are forced to live unnecessarily unhappy, confused, or institutionalized lives."

The senator said older people fail to get mental health treatment for a variety of reasons. Some are reluctant to acknowledge such problems and try to deal with them by themselves, he said. Others are frail and homebound or have transportation problems that prevent them from seeking help. The Medicare system also contributes to the problem, he said, because it does not provide reimbursement for psychologists who provide mental health care.

Rockefeller said that the legislation that he and Coyne are sponsoring would authorize Medicare payments only to well-qualified practitioners. "Only highly-trained and experienced professionals, mental health professionals that are licensed by the state to diagnose and treat mental disorders, would be able to receive reimbursement by Medicare."

HEALTH WEEK

EMERYVILLE, CA
BI-WEEKLY

MAR 6 1989

-8917 BURRELLE'S MX

Lawmakers balancing tight spending with health needs

5603A

By Tinker Ready

HealthWeek Washington Bureau

HEALTH CARE ROUNDUP

- **Medicare:** Lawmakers and White House staffers are meeting on Bush's proposed $5 million cut in Medicare. No compromise yet.
- **Imaging:** Rep. Stark asks HCFA to study the high cost to Medicare of magnetic-imaging services.
- **AIDS in children:** Health officials tell Congress about the problems of children with AIDS and request more collaboration among social service and health agencies.
- **Outlier payments:** Rep. Downey introduces bill to prohibit HCFA from changing its outlier payments policy for at least three years.
- **VA budget:** House committee approves increasing the VA's 1990 budget by $1.3 billion.
- **Overmedication of elderly:** Bill by Rep. Coyne would expand Medicare coverage to include psychological services so elderly who need such help won't rely on drugs instead.

WASHINGTON—As the 101st session of Congress tries to force health care costs down with one hand, the other hand is outstretched, seeking higher funding levels to meet growing public health needs.

Among those pressing needs are:

Medicare

- House and Senate budget committee hearings in February marked the launching of a budget review process expected to continue through summer.

Meetings among key congressmen and White House officials have not produced concrete budget proposals, and Congress appears to be holding its ground against President Bush's proposed $5 billion reduction in Medicare reimbursements.

Members of the House Ways and Means Committee, which oversees the Medicare program, concluded earlier this month that "it is not reasonable to expect providers or beneficiaries to absorb the level of reductions proposed by the administration in the Medicare program." ✓

At the same time, the Catholic Health Association, a trade group here, concluded that the average hospital would lose 11.5 percent on Medicare services if Bush's budget proposals succeed.

Imaging payments

- Rep. Fortney H. "Pete" Stark, D-Calif., has asked the Health Care Financing Administration (HCFA) to look into "exorbitant charges" for magnetic-resonance imaging services.

Stark's request came in response to a New York State Health Department study that found the average cost of an MRI scan is $240, compared with an average charge of $575 to Medicare for the same service.

> ***"At the current reimbursement rates, there will be more MRI centers than McDonald's restaurants, and the resulting overutilization will cost society BILLIONS in unnecessary tests."***
>
> *— Rep. Pete Stark*

The average charge to a privately insured patient, the study found, was even higher—$850.

"At the current reimbursement rates, there will be more MRI centers than McDonald's restaurants, and the resulting overutilization will cost society BILLIONS in unnecessary tests," Stark said in a Feb. 8 letter to HCFA.

AIDS in children

- The federal government produces plenty of studies but not enough funds to fight acquired immune deficiency syndrome in children, Rep. Ted Weiss, D-New York, told top health officials earlier this month.

The health officials were on Capitol Hill to testify before Weiss' Human Resources Subcommittee of the House Governmental Affairs Committee. Antonia Novello, deputy director of the National Institutes of Child Health and Human Development, presented the recommendations of a recent task force study on AIDS in children that included calls for greater collaboration among social service and health agencies.

Rep. Nancy Pelosi, D-Calif., a committee member, criticized Novello for not seeking more funding for the proposed programs in the upcoming 1990 budget. "You're saying to parents, 'Here are some good ideas but they weren't important enough to get into the ground floor of this year's budget,'" Pelosi said.

Novello responded by saying many of the report's recommendations could be initiated with no new funding. About 1.5 percent of the 85,000 people reported as having AIDS are children.

Lower outlier payments

- Rep. Thomas J. Downey, D-New York, introduced a bill that would prohibit HCFA from making dramatic changes in paying for extraordinarily expensive Medicare cases known as outliers.

Last year's change increased payments from one outlier category—those with long stays—to those with extremely high costs regardless of length of stay. The reduced payments hit certain states harder, particularly those with large, low-income populations such as New York.

See CONGRESS, *page 30*

HEALTH WEEK

EMERYVILLE, CA
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CONGRESS

Continued from page 9

Theoretically, the effect is more severe at hospitals reluctant to release low-income patients because they might not receive proper follow-up care at home.

Downey's bill would bar changes to the outlier policy for three years and limit future shifts between the two categories.

VA budget

• On Feb. 22, the House Veterans Affairs Committee unanimously approved an advisory recommendation calling for a $1.3 billion increase in the proposed 1990 Veterans Administration budget and a $520 million increase in the VA's 1989 allocation. Most of the additional funding would bolster VA medical programs, which veterans groups claim are suffering because of severe budget shortfalls.

Overmedication, the elderly

• Legislation to broaden Medicare coverage for psychiatric services would help solve the problem of overmedication among the elderly, officials from the American Psychological Association said earlier this month after the Department of Health and Human Services released a report on the issue.

Some doctors use drugs to treat mental problems in the elderly that could be addressed without medication, the officials said.

Medicare currently covers only psychiatric services provided by physicians. Legislation introduced earlier this month by Rep. William Coyne, D-Penn., would expand coverage to psychologist's services. The House Ways and Means Committee's health subcommittee will hold a hearing on the bill today. ☐

HEALTH WEEK

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Psychologists want Medicare funds

WASHINGTON—Medicare should pay for psychological services for the elderly, the cost of which could reach $25 million by 1993, the American Psychological Association told a recent congressional hearing. The association said 50 percent to 70 percent of the elderly's mental-health needs go unmet, and general practitioners misdiagnose an equal number of mental-health problems. Overprescription of psychoactive drugs compounds the problem, the association said. The American Psychiatric Association opposes such Medicare coverage, arguing that psychologists, who lack medical training, can't handle the medical problems associated with mental illness in the elderly. G60SA

DAILY NEWS

NORFOLK, NE
DAILY 22,294

WEDNESDAY
MAR 15 1989

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136 FT

LaCrosse at Congressional hearing

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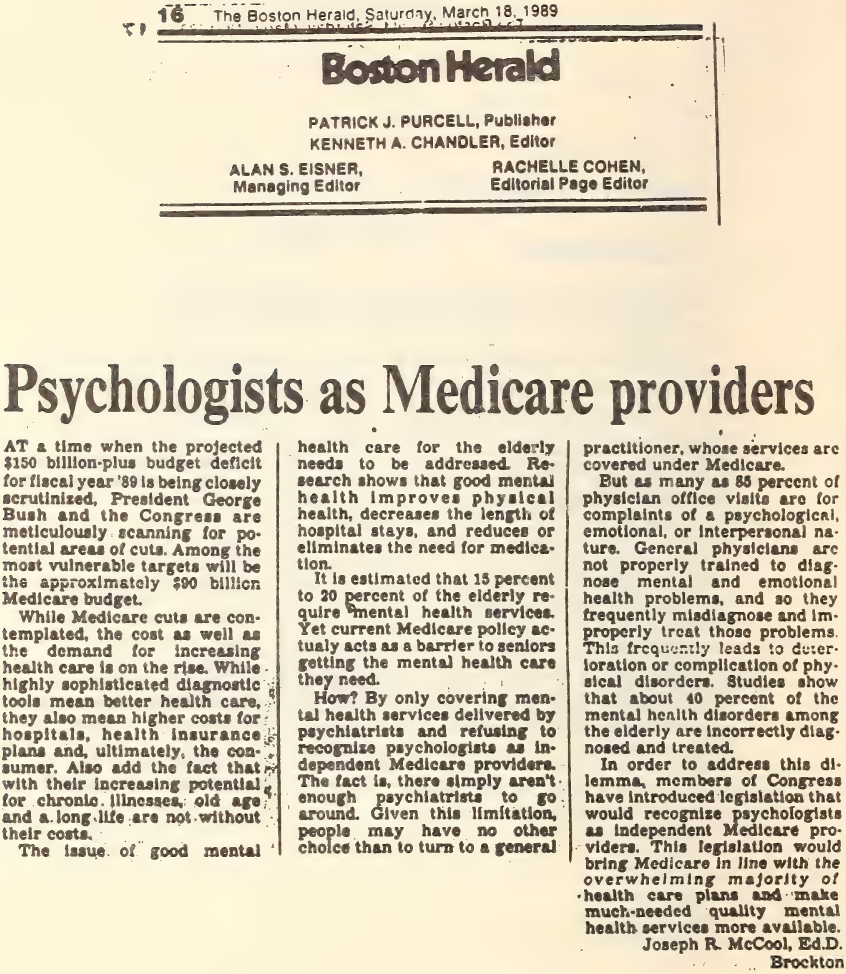
Dr. Michael LaCrosse, clinical director of the Monroe Mental Health Center, has returned from Washington, D.C., where he presented a statement at a hearing sponsored by the American Psychological Association for Congressional staff. It concerned the mental health needs of the elderly, and testimony was provided concerning experiences in Northeast Nebraska of providing psychological health care services to senior citizens.

Many of the psychological health care services being provided in this area are considered to be model services, many of which are yet to be provided to populations in more urban centers throughout the United States.

LaCrosse was in Washington to attend the Board of Professional Affairs meeting of the American Psychological Association. LaCrosse is chairman of the professional affairs committee of the Division of Counseling Psychology. Matters concerning the professional education and preparation of psychologists and the changes that are occurring in the health care environment were major topics of discussion.



16 The Boston Herald, Saturday, March 18, 1989

Boston Herald

PATRICK J. PURCELL, Publisher
KENNETH A. CHANDLER, Editor
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Psychologists as Medicare providers

AT a time when the projected $150 billion-plus budget deficit for fiscal year '89 is being closely scrutinized, President George Bush and the Congress are meticulously scanning for potential areas of cuts. Among the most vulnerable targets will be the approximately $90 billion Medicare budget.

While Medicare cuts are contemplated, the cost as well as the demand for increasing health care is on the rise. While highly sophisticated diagnostic tools mean better health care, they also mean higher costs for hospitals, health insurance plans and, ultimately, the consumer. Also add the fact that with their increasing potential for chronic illnesses, old age and a long life are not without their costs.

The issue of good mental health care for the elderly needs to be addressed. Research shows that good mental health improves physical health, decreases the length of hospital stays, and reduces or eliminates the need for medication.

It is estimated that 15 percent to 20 percent of the elderly require mental health services. Yet current Medicare policy actualy acts as a barrier to seniors getting the mental health care they need.

How? By only covering mental health services delivered by psychiatrists and refusing to recognize psychologists as independent Medicare providers. The fact is, there simply aren't enough psychiatrists to go around. Given this limitation, people may have no other choice than to turn to a general practitioner, whose services are covered under Medicare.

But as many as 85 percent of physician office visits are for complaints of a psychological, emotional, or interpersonal nature. General physicians are not properly trained to diagnose mental and emotional health problems, and so they frequently misdiagnose and improperly treat those problems. This frequently leads to deterioration or complication of physical disorders. Studies show that about 40 percent of the mental health disorders among the elderly are incorrectly diagnosed and treated.

In order to address this dilemma, members of Congress have introduced legislation that would recognize psychologists as independent Medicare providers. This legislation would bring Medicare in line with the *overwhelming majority of* health care plans and make much-needed quality mental health services more available.

Joseph R. McCool, Ed.D.
Brockton

FYI

Saturday, April 1, 1989
The Star-Ledger

READERS' FORUM

Mental health and Medicare

DEAR EDITOR:

President Bush and Congress are grappling with the federal budget deficit, estimated to be between $150 billion and $160 billion for the next fiscal year. The deficit is clearly one of the most urgent problems confronting our country and must be reduced. In the coming months, various proposals will be presented on how to accomplish this goal while, at the same time, attempting to maintain services with "no new taxes."

Medicare, the federal health program for the elderly and disabled, is already a prime target of cost containment. The program costs about $88 billion a year and accounts for about 8 percent of the national budget, with a 10 percent projection by 1993. Some of the recent increases in Medicare spending, however, are due to the growing number of elderly people as well as an adjustment for inflation. Several experts anticipate a proposal from the administration or Congress that would slash approximately $5 billion from Medicare funding.

Cuts in Medicare spending are being recommended at a time when some services to the elderly are clearly inadequate. It is estimated that 15 to 20 percent of the elderly require mental health care which is not now being adequately provided. Drug abuse and suicide rates are particularly high among older persons. Seventeen percent of all suicides are committed by the elderly—a staggering yet not widely known fact. Studies have shown that about 40 percent of mental health disorders among the elderly are being incorrectly diagnosed and treated, frequently leading to deterioration or complications of the patient's accompanying physical conditions. On the other hand, substantial research demonstrates that good mental health care improves physical health, reduces the need for medication, and decreases hospitalizations.

Rather than cutting into Medicare, which provides help for some of our most vulnerable citizens, Congress should explore other ways (and there are many) to improve efficiency and quality of services. Current legislation, sponsored by Sen. Jay Rockefeller (D-W.Va.) and Rep. William Coyne (D-Pa.), along with a number of other bipartisan Senate and House co-sponsors, is aimed at doing just that—improving the efficiency and quality of mental health care for the elderly by recognizing psychologists as independent Medicare providers. At present, Medicare does not offer patients freedom to choose a psychologist as a provider. Should this bill become law, it will provide greater access to much-needed mental health services and provide such services in a cost-effective manner.

In a country whose values emphasize help for the less fortunate, vital services for the elderly, sick and vulnerable must never be sacrificed. Medicare patients face an inordinate amount of psychological stress, anxiety, fear and depression. They deserve the same standard and type of care available to others.

Sen. Frank Lautenberg was a co-sponsor of S-100 last year and we anticipate that he will soon sign on again. I would encourage those of you who are concerned with the mental health needs of the elderly to write to Sen. Bill Bradley, as well as your congressional representatives, urging their support for S-100 or HR-774, the Senate and House versions of the bill, which recognizes psychologists as independent Medicare providers. The bill is cost-effective and improves access to quality mental health care for the elderly. It is simply unfair and wrong to continue to deny freedom of choice to our older citizens with regard to their mental health needs.

Louis B. Schlesinger, President,
New Jersey Psychological Association,
Livingston

Hank Robb, Ph.D.
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THE OREGONIAN, TUESDAY, MARCH 28, 1989

IN MY OPINION

Psychology treatments not covered

By HANK ROBB

A Portland-area physician recently requested that I, as a psychologist, help a 65-year-old woman kick her nicotine addiction, an addiction that kills 350,000 Americans every year. The request could have been for help with depression, anxiety or any number of other psychological difficulties. Unfortunately, I had to remind him that psychiatrists are the only mental health professionals whose services are covered under Medicare.

His immediate response, "That's just nonsense!"

He is right. It is nonsense. This federal restriction is nonsense for two reasons: It drives up the total cost of health care, and it reduces access to mental health care providers.

Since most people don't know the difference between a psychiatrist and a psychologist who diagnoses and treats mental health problems, I'll explain.

Psychiatrists, like other medical doctors, are trained in medicine. Unlike other medical doctors, they are specifically trained to diagnose and treat mental health problems. Because they are medical doctors, they are licensed to prescribe drugs and use other procedures, such as electric-shock treatments, which directly affect the body's physiochemical processes. In turn, these physiochemical changes affect thinking, feeling and behaving.

Psychologists do not use these kinds of interventions. They are trained in psychology and are licensed to diagnose and treat mental health problems using psychological interventions that directly affect thinking, feeling and behaving, but only indirectly affect the body's physiochemical processes.

Confusion on this issue usually results because other medical doctors may prescribe the same drugs prescribed by psychiatrists, and psychiatrists may also use psychological interventions.

Our nation has a $2.6 trillion debt and a budget deficit for the current year of between $150 billion and $160 billion. Medicare is an important but expensive program, ranking third after expenditures for defense and Social Security. Clearly, it is important to control costs in this program, especially at this time.

Instead, the current exclusion of psychologists keeps costs high. On average, psychologists charge 14 percent less than psychiatrists. Studies show that when psychologists directly compete with psychiatrists, psychiatric fees can be reduced up to 12 percent.

Psychologists can provide services less expensively, but current Medicare regulations prevent them from getting reimbursed. The net effect is that Medicare is forced to pay more for services that could be obtained for less.

Health care costs are affected in another way. If left untreated, some people with nervous and mental disorders will develop problems of such severity or complexity that extremely expensive health care treatments, including hospitalization, will be required to help them. Further, research shows that good psychological health has cost-cutting benefits for everyone because it improves physical health, decreases the length of hospital stays and reduces or eliminates the need for medication.

The second reason psychologists should be recognized under Medicare is that psychologists are more accessible than psychiatrists because there are more of them. In the United States there are 48,178 licensed psychologists and only 31,531 licensed physicians trained in psychiatry.

There are no psychiatrists in 62 percent of U.S. counties. They are especially rare in rural areas. However, there is at least one psychologist in each of 622 U.S. counties with no psychiatrist. If Congress allowed psychologists to be compensated under Medicare, the problem of gaining access to a qualified mental health professional would be greatly improved.

Consider the access problem in Oregon. Of our 36 counties, 15 have no physician with psychiatric training. However, five of these counties do have psychologists. And while these five counties are only one-third of the total counties in Oregon without access to a psychiatrist, they contain two-thirds of the people without access to mental health services.

If Congress authorized payment for psychologists, these 18,329 Oregonians 65 years of age or older would immediately have access to qualified mental health professionals within their own counties.

It is time for Congress to recognize psychologists as independent providers under Medicare in order to reduce costs for mental health care services and increase access to mental health care providers. It is time to stop the nonsense and replace it with good sense.

Hank Robb is a Lake Oswego psychologist.

6A The Cedar Rapids Gazette: Fri., April 28, 1989

The Gazette

An independent newspaper established in 1883

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OPINION

Mental health care: Often unmet need

RONALD G. NELSON

of Cedar Rapids is a licensed clinical psychologist who spends half his professional time at the Abbe Center for Community Mental Health.

The Bush administration and Congress face an enormous task in balancing the federal budget. Major budget cuts targeting Medicare are proposed to cut care to one of our nation's fastest growing populations — the elderly. Rather than cutting Medicare programs arbitrarily, Congress must explore creative ways to improve the efficiency and quality of Medicare services.

One area worth exploring is mental health services. Research demonstrates that good mental health care improves physical health, reduces the need for medication and decreases hospital stays.

Psychologists can provide quality mental health care to the 50 to 70 percent of the elderly whose current mental health needs are unmet. It is well documented that psychological intervention can result in significant reductions in medical costs. This is a critical point when addressing how to be more cost efficient under Medicare.

Psychologists are not included as independent providers under Medicare, except in rural health clinics and community mental health centers.

The primary providers for mental health services under Medicare are general physicians who, on average, have less than three months of training in mental health care. If psychologists were identified as providers in Medicare, mental health services would become much more accessible to the elderly.

Medicare legislation under consideration in the House and Senate would allow the elderly to access psychologists for their mental health needs. Psychiatrists — the only recognized mental health professionals under Medicare — are not included in two-thirds of U.S. counties. Psychologists can meet the needs of over 30 percent of this population.

In Iowa, psychiatrists are not found in 71 percent of the counties. The counties with no psychiatrists have a higher percentage of rural residents and have a greater proportion of residents over 65 years than in any state as a whole.

Twenty-one Iowa counties have psychologists and no psychiatrists. These 21 counties have nearly one-half million people of whom 14.7 percent, or 62,927 people, are over age 65. Full recognition of psychologists under Medicare will help the elderly gain access to qualified mental health professionals and to much-needed services.

It is estimated that 15 to 20 percent of the elderly require mental health services. Drug abuse and suicide rates are particularly high among older persons. Seventeen percent of all suicides are among the elderly.

In counties where psychiatrists are not located, general physicians are providing these services. Often they do not have the time or appropriate experience and training to treat complex mental disorders. Also, many of the elderly's physical concerns are masking underlying emotional needs.

The Congressional Budget Office has estimated start-up costs for recognizing psychologists as Medicare providers at $10 million — only .01 percent of total Medicare costs. This does not reflect cost savings resulting from lower cost mental health services or the cost saving resulting from reduced medical care utilization.

Our nation's elderly deserve the right to quality health care services to fulfill lives of dignity in their older years. Cutting Medicare services may unnecessarily burden the millions of elderly who depend on these services. Legislation expanding services to include psychologists as Medicare providers improves efficiency and quality of these services.

Pittsburgh Post-Gazette

WEDNESDAY, MARCH 29, 1989

LETTERS TO THE EDITOR

Psychology of aging

Last month your health writer Henry Pierce wrote about the positive influence of "healthy attitudes" on physical health. He cited recent research in brain chemistry that suggests a link between emotional state and the body's immune system. Studies found that stress reduction, a positive outlook and a sense of coping are coupled with better immune function. One study demonstrated a difference between patients who received psychological help and those who did not.

The consistency of like findings over many years supports the place of mental-health treatment in total health care.

There is a group in our society especially vulnerable to the negative effects of attitude on health. They are the ones who face the psychological and social problems that come with aging. Research of Dr. Leon Kalson, a Pittsburgh psychologist, shows that self-image suffers as various social roles disappear. Retirement, loss of a spouse, scattered families and the deaths of acquaintances eliminate one's identity as worker, spouse, grandparent, parent and friend. The elderly tend to lose self-esteem and accept negative stereotypes.

Depression is a leading mental-health problem in the older population. Seventeen percent of all suicides are among the elderly.

The institution, with its inevitable depersonalization and overreliance on anti-psychotic drugs, was often the only alternative for the distressed elderly. Now, with the development of effective behavior therapies, many can be helped through psychotherapy to remain active and independent in their later years.

Despite the evidence of an unmet need, Medicare does not currently recognize a sufficient number of appropriately trained mental-health providers. Psychiatrists are the only mental-health professionals whose services are covered, yet there are no psychiatrists in 62 percent of the nation's counties.

Some members of Congress are hoping to correct the deficiency. Rep. William Coyne of Pittsburgh and Sen. Jay Rockefeller of West Virginia are sponsoring legislation to increase older persons' access to quality mental-health care by recognizing psychologists as independent Medicare providers.

Changing the Medicare law to recognize psychologists would not only offer mental-health services to those who now have no access to quality care but it would also increase the availability of lower-priced providers to all Medicare beneficiaries. On the average psychologists charge 14 percent less than psychiatrists.

This legislation is especially important for Pennsylvania, which has the fourth-oldest population of any state.

ZITA LEVIN
Greater Pittsburgh
Psychological Association
Churchill

Sunday, March 19, 1989 The Pittsburgh Press B3

LETTERS

Tax reform a sham

The so-called "Tax Reform Act" on which the voters of Pennsylvania will vote in the May primary is nothing more than another tax increase.

If this amendment to the Pennsylvania Constitution is approved by the electorate, the retired senior citizen, who has been thrifty and managed to accumulate a small savings account or money market fund, will be the hardest hit once again.

The local municipalities and school districts, which are now permitted to impose a maximum 1 percent wage tax only on earned income, would be allowed to collect a total of 2.25 percent on all income such as wages, interest, dividends and net profits on any income.

If the local taxing body imposes this tax, it will be required to throw a bone to the property owner by reducing his property tax millage by 25 percent.

This is a sham in that the county assessor's office sets the individual property value. The local taxing body then multiplies the county assessed value by the millage rate to arrive at the property tax.

Who controls the county assessor's office? Need I ask?

Additionally, the local taxing body, if it imposes this new tax, will be required to cut the property tax only for the first four years. What is to prevent this taxing body from restoring this 25 percent cut after four years? Would you care to venture a guess?

This referendum should receive a resounding "NO!"

ALTON A. KESTER
Green Tree

Mental aid needed

With the current budget deficit estimated at $150 billion to $160 billion, the new administration and Congress are searching for optimum cuts in 1990.

Medicare will again seem like a fair target. Its projected $88 billion cost this year is 8 percent of the pie, predicted to be 10 percent in 1993.

At first glance, solutions to increasing Medicare costs seem easy. Make another cut in reimbursement to hospitals, cap physician's fees, disallow payment for services that officials consider unnecessary, raise premiums for the elderly.

But each approach carries risks that could close the doors to Medicare patients in some places or reduce the quality of their care.

While every economy is worth considering, maybe more attention should be given to improving the efficiency and quality of the system. One way is to make mental health services more available.

Aging in today's society can cause a host of psychological and social problems. Dr. Leon Kalson, a local psychologist in private practice, found in his research that self-image suffers as social roles disappear.

Retirement, loss of a spouse, scattered families, and the deaths of acquaintances eliminate one's identity as worker, spouse, grandparent, parent, and friend. The elderly tend to lose self-esteem and accept negative stereotypes.

When you consider the facts, the need for improved access to qualified mental health professionals is clear. An Allegheny County study in 1986 revealed that depression is a leading mental health problem in the older population.

In the past, older persons with emotional or psychological problems brought on by life's adversities faced institutionalization, often coupled with over-medication. Now there is increasing evidence that mental health therapy can help to keep people active and independent through their later years.

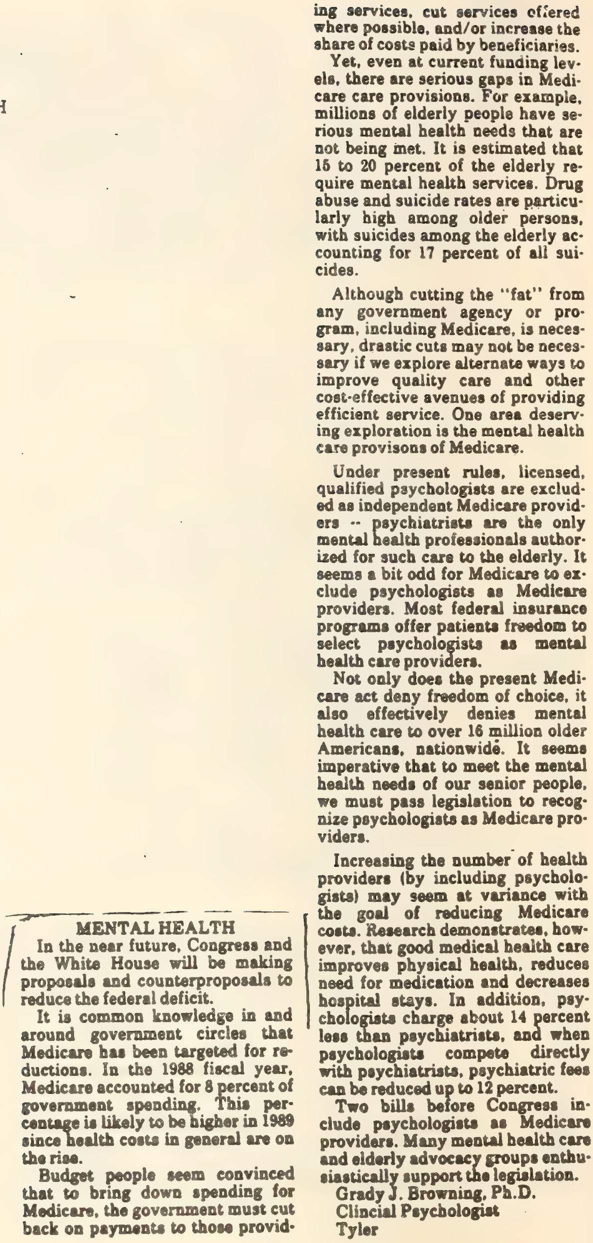
U.S. Rep. William Coyne of Pittsburgh and Sen. Jay Rockefeller of West Virginia are sponsoring legislation to improve older persons' access to quality mental health care by recognizing psychologists as independent Medicare providers.

ZITA LEVIN
Churchill

(The writer is a member of the Greater Pittsburgh Psychological Association task force on Medicare services.)

TYLER MORNING TELEGRAPH

Tyler, Texas
March 16, 1989



MENTAL HEALTH

In the near future, Congress and the White House will be making proposals and counterproposals to reduce the federal deficit.

It is common knowledge in and around government circles that Medicare has been targeted for reductions. In the 1988 fiscal year, Medicare accounted for 8 percent of government spending. This percentage is likely to be higher in 1989 since health costs in general are on the rise.

Budget people seem convinced that to bring down spending for Medicare, the government must cut back on payments to those providing services, cut services offered where possible, and/or increase the share of costs paid by beneficiaries.

Yet, even at current funding levels, there are serious gaps in Medicare care provisions. For example, millions of elderly people have serious mental health needs that are not being met. It is estimated that 15 to 20 percent of the elderly require mental health services. Drug abuse and suicide rates are particularly high among older persons, with suicides among the elderly accounting for 17 percent of all suicides.

Although cutting the "fat" from any government agency or program, including Medicare, is necessary, drastic cuts may not be necessary if we explore alternate ways to improve quality care and other cost-effective avenues of providing efficient service. One area deserving exploration is the mental health care provisons of Medicare.

Under present rules, licensed, qualified psychologists are excluded as independent Medicare providers -- psychiatrists are the only mental health professionals authorized for such care to the elderly. It seems a bit odd for Medicare to exclude psychologists as Medicare providers. Most federal insurance programs offer patients freedom to select psychologists as mental health care providers.

Not only does the present Medicare act deny freedom of choice, it also effectively denies mental health care to over 16 million older Americans, nationwide. It seems imperative that to meet the mental health needs of our senior people, we must pass legislation to recognize psychologists as Medicare providers.

Increasing the number of health providers (by including psychologists) may seem at variance with the goal of reducing Medicare costs. Research demonstrates, however, that good medical health care improves physical health, reduces need for medication and decreases hospital stays. In addition, psychologists charge about 14 percent less than psychiatrists, and when psychologists compete directly with psychiatrists, psychiatric fees can be reduced up to 12 percent.

Two bills before Congress include psychologists as Medicare providers. Many mental health care and elderly advocacy groups enthusiastically support the legislation.

Grady J. Browning, Ph.D.
Clincial Psychologist
Tyler

Richmond Times-Dispatch

JOHN STEWART BRYAN III
Publisher

EDWARD GRIMSLEY
Editor of the Editorial Page

ALF GOODYKOONTZ
Executive Editor

MARVIN E. GARRETTE
Managing Editor

Tuesday, May 2, 1989

Medicare Should Include Psychologists' Services

The new administration and Congress are gravely concerned about the country's growing deficit, estimated at between $150 billion and $160 billion for 1989. In their attempts to find ways to reduce this deficit, health care has been designated as a likely target for significant budget cuts.

Rather than cutting the Medicare budget, Congress should explore ways to improve the efficiency and quality of care provided. One area where this is clearly needed is mental health care. The elderly have serious mental health care needs that are not being met. An estimated 15 to 20 percent of the elderly require mental health services. Drug abuse and suicide rates are particularly high among older persons, with 17 percent of all suicides occurring among the elderly. Yet despite this obvious need, current Medicare policy actually reduces access to qualified mental health professionals.

Psychiatrists are Medicare's only authorized mental health providers. However, there are no psychiatrists in 45 percent of Virginia's counties.

In the absence of qualified mental health professionals, individuals frequently turn to general physicians who do not have adequate training in diagnosing and treating mental disorders. In fact, about 40 percent of mental health disorders among the elderly are incorrectly diagnosed and treated, leading to deterioration or complication of other medical problems — ultimately costing insurance plans added medical expenses.

Recognizing psychologists as independent Medicare practitioners will improve the accessibility of mental health care to the chronically ill and elderly.

Legislation to include psychologists in Medicare is presently being considered in both the Senate and House of Representatives. The Congressional Budget Office has estimated that the start-up cost to allow direct access to psychologists is $10 million. This represents only .01 percent of the total Medicare costs and does not include cost savings resulting from the reduction in overall medical utilization.

ROBERT J. RESNICK, Ph.D.,
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